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# THE POTASSIUM AND WATER CONTENTS OF CAT NERVES AS AFFECTED BY STIMULATION

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A LOSS of potassium from unmyelinated crab nerve has been reported by Cowan ('34) and has been recently confirmed with somewhat improved technique by Young ('38). Vogt ('36) has reported losses of K from the cervical sympathetic ganglion during stimulation. No observations have apparently been made on myelinated nerves except two experiments (Fenn, '34) on frog nerves which showed only losses of K and of Cl too small to be significant. In this paper experiments are reported on the sciatic nerve of the cat. In part, the observations were incidental to other experiments on the loss of potassium from cat muscle (Fenn and Cobb, '36) when stimulated through its nerve.

## METHODS

While details differed in the various experiments, the usual procedure consisted in cutting the sciatic nerve on both sides of the cat as far centrally as possible and stimulating on one side through shielded silver electrodes with either a continuous or intermittent tetanus for 30 minutes or more. The branch of the nerve supplying the hamstring muscles was cut. After stimulation, the animal was bled to death and both sciatic nerves were dissected out, omitting 2 cm. at the central end which had been between or just below the electrodes. The tibial branch was dissected out to the gastrocnemius muscle and the superficial peroneal to the ankle. Both nerves were treated as much alike as possible during the dissection, with care to avoid undue drying and inclusion of any of the surrounding tissues. The nerves were weighed fresh in weighing bottles, dried at 100°C. to constant weight, ashed in a muffle furnace at 500°C. and analyzed for potassium by a slightly modified Shohl and Bennett method. Each nerve weighed about 0.5 gram and contained about 0.8 mgm. of potassium, an amount well within the range of the method. The accuracy of the analyses for which I am mostly indebted to my assistant, Mrs. Doris Cobb Marsh, has been checked in many previous investigations. The average difference between the potassium contents of paired nerves has been found to be 2 per cent (Fenn and Cobb, '35). A single control experiment in which both nerves were unstimulated showed changes as large as those usually observed in stimulation experiments and indicated that nothing could be gained by a more extensive control series.

## RESULTS

A total of twenty-four experiments were completed and the results are summarized in Table 1. The water and potassium contents of the resting nerves were quite variable, presumably because of varying amounts of myelin

sheath, fat, and connective tissue. The potassium figures were equally variable, whether calculated per 100 grams of nerve water or per 100 grams of dry tissue, so that the variation was not all due to different amounts of non-aqueous solid material, but partly due, presumably, to varying amounts of axones.

TABLE 1  
*Summary of twenty-four experiments*

	Normal content	Probable error of mean	Range	Change due to stimulation	Out of 24 cases
Water: cc. per 100 gms. dry	196.0	$\pm 2.1$	164-240	$+5.6 \pm 2.1$	14 gains
Water: cc. per 100 gms. wet	66.2	$\pm 0.07$	62- 70	$+1.9 \pm 0.7$	14 gains
Potassium: m.-eq. per 100 gms. dry	14.1	$\pm 0.2$	11- 17	$+0.09 \pm 0.19$	10 gains
Potassium: m.-eq. per 100 gms. water	7.3	$\pm 0.09$	6.4-8.5	$-0.15 \pm 0.06$	17 losses

The changes in water and potassium caused by stimulation were in general small, and none of the average changes shown in the table were really significant as indicated by the probable errors of the means which are included in the table. In general, about half of the nerves showed gains and half losses. The most nearly consistent result was obtained from the potassium changes calculated per 100 grams of nerve water. The figures showed that seventeen out of twenty-four nerves lost potassium but the average loss was only 2.5 times the probable error. If there is any loss of potassium, therefore, it amounts to less than 2 per cent and is too small to be detected with certainty by this method.

While a statistical study shows that the changes observed on stimulation were not significant, some of the changes were too large to be accounted for purely by the analytical error. The largest of these were losses of both potassium and water, or gains of both potassium and water (per 100 grams of dry weight) amounting to 15-25%. Such results might be due to the inclusion of more nonaqueous material with one of the nerves than with the other; they were particularly evident in the first few experiments where the dissection may have been less skillful. Moreover, the ratio  $\Delta H_2O/\Delta K$  in these extreme cases was closely similar to the ratio of  $H_2O/K$  in the original nerve. Other occasional variations were probably attributable to some experimental error. Many attempts were made to obtain more consistent results by varying the nature of the stimulation, or the condition of the animal, or by better preservation of the blood supply of the nerve, but the results were always disappointing.

It is necessary to conclude, therefore, that any mobilization of K or gain of  $H_2O$  which may occur is so delayed by the medullary sheath that the net change is inappreciable. Or the change due to each impulse is so small that recovery is complete before the arrival of the next one. It is also possible that the electrolyte changes are purely secondary phenomena, dependent upon the

recovery processes so that conduction can occur in cat nerves without a loss of potassium

#### SUMMARY

Cat nerves stimulated continuously in situ for 30 minutes or more at a frequency of 50-100 per second show no consistent loss or gain of potassium or water.

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# THE EFFECT OF STIMULATION ON THE POTASSIUM CONTENT OF LIMULUS LEG NERVES

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THE RESULTS of experiments on the potassium loss in nerves during stimulation have led to no definite general conclusion. Fenn ('38) working with the myelinated nerves of cats and frogs obtained no significant loss of potassium. Cowan ('34) using the unmyelinated nerves of the spider crab, *Maia squinado*, obtained an appreciable loss of potassium during fifteen minutes of stimulation. His method, however, is open to two criticisms: (1) The sections of nerves from which the potassium was lost, were between the stimulating electrodes. (2) No criterion was used to determine whether the nerves were conducting during stimulation. It seemed important therefore, to determine again the effect of stimulation on unmyelinated nerve with appropriate modifications of the technique.

## METHOD

Initially, experiments were started using the nerves of the spider crab, *Libinia emarginata*, but were discontinued due to the rapid loss of excitability. The leg nerves of *Limulus polyphemus* were then chosen since they could be easily dissected out and retained their excitability, provided the enclosing vascular sheath was not removed.

The legs were cut off at their junction with the body, threads were tied around the proximal end of the nerves, and the nerves dissected from all but the two most distal segments of the legs. These preparations were kept in running sea water for at least one-half hour before using. Corresponding nerve-muscle preparations from the opposite sides of the animal were used as experimental and control preparations respectively.

The two preparations were placed in a dish of sea water and the claw of the experimental preparation was connected to an isometric lever. The experimental nerve was then stimulated at a frequency of one hundred and fifty shocks per second for fifteen minutes or more, by means of a thyatron stimulator. The tension maintained by the claw dropped to about 50 per cent of its initial value after fifteen minutes stimulation. The control nerve was tested at the beginning and end of stimulation, and only those preparations which showed contraction of the claw and abduction at the first joint were used.

After stimulation, the nerve of the experimental preparation was cut where it entered the second joint, and again just distal to the stimulating electrodes. It was then blotted on filter paper; weighed on a torsion balance, and trans-

ferred to a weighing bottle. The corresponding section of the control nerve was excised and treated similarly.

After drying to constant weight at 100°C. the nerves were analyzed for potassium using the modification of Shohl and Bennett's method described by Fenn and Cobb ('36).

Twenty-three pairs of nerves were analyzed. Of these, four experiments were discarded for obvious technical errors. Of the remaining nineteen, three had no dry weight determinations.

The results of these experiments are:

Average per cent loss of potassium =  $3.15 \pm 2.1$  (P.E. of mean) Calc. on wet wts. 19 expts.

Average per cent loss of potassium =  $4.2 \pm 1.7$  (P.E. of mean) Calc. on dry wts. 16 expts.

The above results are hardly significant, probably because of dissimilarity in control and stimulated nerves. A suitable procedure for eliminating those preparations in which control and stimulated nerves are different seems to be on the basis of comparison of dry wt./wet wt. between the control and stimulated preparations.

In the above sixteen experiments with wet and dry weights the average per cent difference of the ratio dry wt./wet wt. is  $0.2 \pm 1$  (P.E. of mean) indicating no significant change in water content in either direction as a result of stimulation. Three of the above pairs however, had differences in the ratios (dry weight/wet weight) of -12.8 per cent, 9.3 per cent and 10.2 per cent respectively. These differences are so large compared with the probable error of the average of this ratio that they could only have been due to very dissimilar control and experimental preparations. There is justification therefore for omitting these three experiments also.

For the remaining thirteen experiments, eleven of which showed a loss as indicated in Table 1, the average per cent loss of potassium was:

(a)  $6.1 \pm 1.2$  (P.E. of mean) calc. on wet wts.

(b)  $7.0 \pm 1.2$  (P.E. of mean) calc. on dry wts.

The averages of Cowan's results for a 15 minute stimulus on *Maia* nerves as calculated from his paper are:

Loss of potassium at 40 shocks per sec. = 5.9 per cent based on wet wts.

Loss of potassium at 100 shocks per sec. = 7.4 per cent based on wet wts.

Loss of potassium at 140 shocks per sec. = 6.9 per cent based on wet wts.

#### SUMMARY

Analyses for potassium in the leg nerves of *Limulus polphemus* showed a loss of six to seven per cent of the potassium during a tetanus of fifteen minutes. This is in agreement with the results of Cowan on the loss of potassium from the leg nerves of *Maia squinado*.

Acknowledgments are due to Mrs. Doris Cobb Marsh for the potassium analyses, to Dr. W. O. Fenn who initiated the experiments, for his advice and assistance, and to Dr. M. H. Jacobs for extension of facilities at the Marine Biological Laboratory.

TABLE 1  
*Weights and potassium contents of limulus nerves*

Wet wt. mgms.		Dry wt. mgms.		Potassium mgm. % wet wt.	
Control	Stimulated	Control	Stimulated	Control	Stimulated
132	105	17	13.5	510	544
51	53.5	9.8	10.8	446	360
70.5	75	12.2	13.0	561	486
138	136	22.9	22.3	409	369
151	137	26.7	23.4	380	388
119	118	21.0	20.5	379	347
80	81.5	13.4	14.0	436	431
127	140	21.4	23.1	444	386
130	115	20.6	19.4	434	423
*52	54	17.9	18.1	735	683
65	72.5	10.0	11.8	546	513
95.5	88.5	15.1	13.5	506	454
72.0	67	13.0	12.5	488	486

\* Sheaths dissected off before weighing and analyzing.

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# THE NON-CENTRIFUGAL DEGENERATION OF SEVERED PERIPHERAL NERVE

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(Received November 3, 1937.)

## INTRODUCTION

NEUMANN in 1868 proposed the idea that severed peripheral nerve degenerates centrifugally; i.e., the degenerative processes start at the cut end and progress slowly towards the periphery. This view, opposing the conception of simultaneous degeneration advanced by Lent in 1856, started a controversy as yet unsettled. Most of the arguments on both sides have been based on histological evidence—only relatively recently has there been any physiological experimentation on the subject. The early physiological studies were concerned chiefly with the time of disappearance of indirect excitability of the muscles innervated by cut nerves (Bethé, 1903; Courricr, 1926).

Apostolaki and Deriaud (1925) found no change in chronaxie following section until the "complete degeneration" of the nerve (i.e., loss of indirect excitability of the muscle). This occurred by 9-10 days in frogs kept at 12-15°C. The nerve's rheobase increased by the fourth day after the cut, but there was no appreciable change in gastrocnemius chronaxie for 20-30 days. Titeca (1932, 1935) confirmed this for frogs kept at 22°C. (no change in chronaxie for 8 days). He also described an early "fatiguability," manifested as an increasing threshold with repeated stimulation. This was found to progress slowly centrifugally and was correlated by him with Parker's observations on centrifugal degeneration of motor fibers of the frog sciatic (Parker, 1933) and of myelin sheaths of the lateral line nerves of catfish (Parker and Paine, 1934). On the other hand, Titeca reported that action potentials disappeared simultaneously all along the degenerating frog nerve. Koch (1925) had earlier shown a uniform loss of resting potential throughout degenerating mammalian nerve.

More recent experiments on rats and frogs (Holobut and Jalowy, 1936) again showed no change in chronaxie until loss of indirect excitability, and the uniform loss of action potential along a cut nerve (indirect excitability disappeared at 6-9 days at a temperature of 10-12°C.; Holobut, 1937).

In view of the discrepancy between the action potential findings, which indicate simultaneous degeneration of frog nerve, and the evidence for centrifugal degeneration obtained from twitch heights, histology, and fatiguability, it seemed desirable to study several of these attributes on the same preparations.

## METHOD

Winter and spring frogs (*Rana pipiens* and *R. sylvatica*) were kept in a large tank, with a constant flow of water sufficient to maintain a layer half a centimeter deep. Only healthy animals were used. Under light ether anesthesia, the skin on the back was cleaned

with alcohol, an incision, about 1 cm. long, made between the urostyle and the ilium, the underlying muscles separated with fine-pointed forceps, and the sciatic plexus revealed. Avoiding adjacent blood vessels, the left sciatic trunk was picked up on a pair of curved forceps and sectioned with sharp scissors just below the anastomosis of the spinal nerves. The cut ends of the nerve were allowed to slip back, the muscles drawn together, and the lining of the dorsal lymph sac and the skin were closed, usually together, with one or two silk sutures. In most cases, healing occurred rapidly: infected animals and those which developed red leg were discarded.

In the first series, frogs were kept at a temperature between 18°C. and 20°C.: in the second, between 12°C. and 15°C. For these longer experiments, the frogs were forced-fed with small bits of chopped meat. Only those animals vigorous at the time of examination were used.

From 1 to 20 days after operation, a frog was pithed and immobilized, and both sciatic nerves dissected free without injury to the blood vessels of the leg. In all experiments, the left (operated) and right (control) nerves were treated alike as far as possible. For the kymograph records the usual gastrocnemius-muscle-lever set-up was used except that the femoral end of the muscle was left intact so that its circulation remained unimpaired and the bone was clamped *in situ*. In a number of experiments records were taken simultaneously from the gastrocnemius and from the peroneal group of muscles. The same length lever arms were used with both right and left sides to permit a roughly quantitative comparison.

The nerve was stimulated using bipolar metal electrodes 1 mm. apart from a Harvard inductorium with 6 volts in the primary and with the secondary, to start with, at 13 cms. and an angle of 5° from vertical. In no case was it necessary, in order to get maximal responses, to have the coil horizontal at less than 9 cms. The electrodes were placed at three positions: H, 1-2 cms. below the cut end (to avoid the area of traumatic degeneration), M, just before the bifurcation of the sciatic to form tibialis and peroneal nerves, and, K, at the knee. Each region was tested in order with progressively stronger stimuli, from subthreshold to slightly supramaximal. To minimize as much as possible the inevitable fatigue (which is more pronounced in the operated nerve), the whole preparation was repeatedly washed with Ringer's solution. This procedure eliminated bizarre results found in preliminary experiments, such as a period of inexcitability between two periods of good excitability.

After muscle responses were recorded, the nerves were removed and their action potentials studied with the cathode-ray oscillograph (Gerard, Marshall, and Saul, 1936). The trace was sometimes photographed, more often measured on the screen. A standing wave was obtained by using a commutator interrupter in the primary of the inductorium. The central end of the nerve was placed on stimulating electrodes and a pair of silver lead electrodes, 1 cm. apart, moved along the nerve. Change of spike height with distance was compared for normal and sectioned nerves.

In a few cases, with conduction on the verge of failing, extensive kymograph records were omitted and only tests for the presence of indirect excitability carried out before removing the nerve. Other frogs from the same batch and in the same operative period were then used for the contraction height measurements. This was necessitated by the excessive fatigability of such nerves.

In all cases, following these tests, the nerves were examined histologically.\* A few were washed, teased, and immersed in 1:10,000 neutral red, according to the method of Covell and O'Leary (1932). The majority were fixed in 10 per cent formol in 0.7 per cent NaCl or in H<sub>2</sub>O, teased, and stained with a modified Herxheimer stain by the following procedure:

1. Cover slide upon which nerve is teased with Sudan III (Romeis, 1929) for ten minutes
2. Wash rapidly (distilled water) until wash water is almost clear
3. Flood with 1% aqueous haematoxylin for five minutes
4. Wash off excess stain with distilled water
5. Flood with 1 per cent ferric chloride for 1-5 minutes, depending on intensity of stain desired
6. Wash well with tap water
7. Mount in glycerine jelly, after complete teasing of nerve.

\* The neutral red stain was not used because it is held (Cajal, 1928) not to show accurately the changes in the early stages of degeneration.

The whole process is carried out on the slide: with practice the nerve does not come off. Final teasing with steel needles or quills under a strong dissecting microscope clearly exposes individual nerve fibers for comparatively long distances (1-2 cms.). The myelin products appear orange-red, the nucleus and cytoplasm deep blue, and, if washing was adequate, the preparation lasts at least two months.

Camera lucida drawings were made of significant preparations.

In all, over 75 frogs were examined 2-20 days after nerve section, and of these about a third in 12-16 days, the period supposed to show progressive degeneration most clearly. To eliminate the possibility of missing any progressive degeneration because of too rapid degeneration at 18°-20°C., a second series of frogs was run at 12°-15°C. Except for a prolonged time scale in the latter case, the results in the two series were the same. In addition, a series of 8 rats was run to confirm the simultaneous degeneration of mammalian (monkey and cat) sciatic nerves described by Heinbecker, Bishop, and O'Leary (1932).

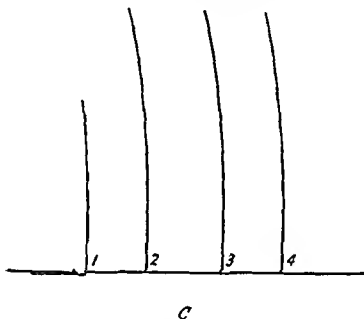


FIG. 1. Kymograph records of gastrocnemius twitches caused by stimulation of a normal sciatic nerve with submaximal shocks (secondary at 13 cms., 5° from vertical), showing the shunting effects of branches.

1. Tibialis nerve central to muscular branch.
2. Tibialis nerve peripheral to muscular branch.
3. Same as 1, after stripping back muscular branch.
4. Same as 2.

## RESULTS

When adequate stimuli are applied to various points along the sciatic nerve, the gastrocnemius contracts to the same degree for all electrode positions. The contrary findings of Parker, indicating centrifugal degeneration, seem due to the use of stimuli which were partly submaximal for one of three reasons.

The motor fibers do not run together as a bundle in the center of the sciatic nerve, but rather pass from a loose accumulation of fibers on the dorsal side of the nerve in the proximal stretch to a denser group on the medial-ventral side more distally (Kurkowsky, 1935). With the secondary coil at 13 cms.

and 5° from the vertical, a stimulus is delivered which is not strong enough to excite all the motor fibers unless the electrodes are placed directly on them. It is clear that stimuli which are adequate in one region of the nerve may not be so in another. Further, the eccentric course of the motor fibers makes any twisting of the nerve upon the electrodes of extreme importance. Finally, still with submaximal stimuli, confusing results are obtained when the fiber distribution is altered by branches leaving the main trunk between different regions of stimulation.

These points are illustrated by results on a normal nerve. With stimuli of the strength indicated, the contraction was less with electrodes on the hip region of the nerve than when they were at the knee, while with stronger stimuli the responses from both regions were equal (Fig. 1). This is the result Parker (1933) obtained on a degenerating sciatic nerve. In these experiments,

TABLE 1

*Protocol of contraction heights of muscle twitches resulting from stimulation of degenerating frog sciatic cut eight days previous to experiment. Temperature 12°-14°C.*

Stimulus strength	Stimulus position					
	Hip		Middle		Knee	
	Over <sup>1</sup>	Under	Over	Under	Over	Under
Weak (13 cm., 70°)	(14) <sup>2</sup>	52	65	30	60	75
Medium (13 cm., 0°)	33	90	83	(78)	(86)	(95)
Strong (9.5 cm.)	100	100	100	100	100	100

<sup>1</sup> Over indicates electrodes were held on top of nerve; under indicates electrodes were held under nerve: in both cases, without regard for true dorso-ventrality of the nerve trunk.

<sup>2</sup> Numbers give contraction height in per cent maximal. Those in parentheses indicate proportionate values interpolated from duplicate experiment.

also, with weak stimuli peculiar responses can be obtained from various nerve levels (and with twisting of the nerve), whereas with adequate stimuli, the responses from all levels of the nerve are the same (Table 1). There is especial danger of using inadequate stimuli on a degenerating nerve because there is a progressive increase in threshold from day to day. (This is independent of the decreased response to a maximal stimulus as more and more fibers become fully inactive.) But when adequate stimuli are used, muscle twitches of constant height result from stimulation at any level of the nerve. Further, the rise in threshold, increase in fatiguability, and falling off of contraction all progress with the duration of degeneration simultaneously along the entire cut nerve.

Current spread from a less excitable central region to a more excitable peripheral one is ruled out by the following experiment: with continued stimulation at H, the muscle response falls to zero due to local nerve fatigue. Stimuli applied at K are still fully effective at this time. With rest, H stimuli recover their full action. Clearly no significant stimulus spread could occur.

Complete loss of indirect excitability occurred about the thirteenth day at 18°-20°C.; about the seventeenth day at 12°-15°C. (Table 2), in the frogs. In the rats (male albino), loss of indirect excitability took place between 50 and 70 hours after operation.

The peculiarities in motor fiber distribution do not significantly influence the oscillograph records. It was found that action potentials declined with time and disappeared simultaneously at all points along the degenerating nerve, as has been clearly shown also by Titeca (1935).

With adequate stimuli, then, and regard for anatomical peculiarities of the nerves, physiological tests show that functional degeneration occurs simultaneously throughout a cut, degenerating, peripheral nerve.

TABLE 2

*Loss of indirect excitability of gastrocnemius with increasing period of degeneration of cut sciatic*

Temperature	18°-20°C.		12°-15°C	
Number of frogs	41		19	
Days since cut	+	-	+	-
2- 8	16	0	2	0
9	3	0	2	0
10	2	0		
11	1	0	2	0
12	3	0		
13	2	1	2	0
14	0	3		
15	0	1	2	0
16	0	3	2	0
17-20	0	6	0	7

+ Indicates visible response to stimulation

- Indicates lack of visible response to stimulation, starting with weak stimuli, and ending with coil distance of 6 cms

The histological findings also agree, for, as Ranson, Cajal, and others have emphasized, when the region of traumatic degeneration near the plane of section of a peripheral nerve is eliminated from consideration, degeneration of the myelin sheaths proceeds in all parts of the nerve at once. An incomplete histological examination of degenerating nerve, however, can be very misleading. In different fibers at one level, nodes may vary from normal to completely degenerate; but in one individual fiber, though the condition is not the same at all levels, the variation from place to place is much less than that from fiber to fiber at one level. Fig. 2 was taken from a nerve cut four days previously, hence too early for observing progressive degeneration. It is obvious that the nodes of the three figured axones are different—varying from the essentially normal condition in fiber c to the moderate degeneration of fiber a, shown by the widened node, clearly visible axis cylinder, and beginning myelin globule formation. In like manner, the internodes at the level of the Schwann cell nucleus are respectively normal or fragmented. The signs of degeneration were equally present throughout a 9 mm. length of fiber a (teased out), and absent throughout a similar length of c.



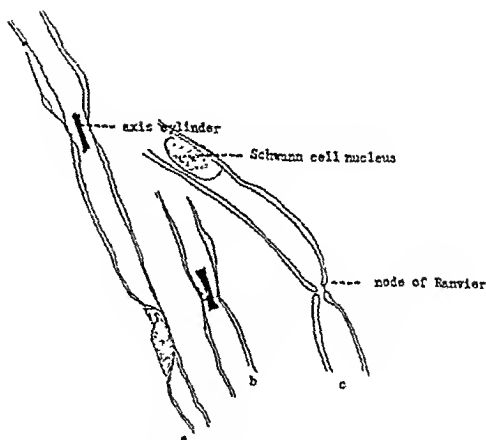


FIG. 2. FNS 4. Left sciatic cut 4 days previously.  $T = 18^{\circ}$ – $20^{\circ}\text{C}$ . At this level, the condition of the nodes is not the same in individual fibers: in fiber a, the nodes are approximately the same throughout 8 mm.—there was no gradation towards the more normal node of fiber c. Fiber b represents a somewhat intermediate stage.

Drawings made with camera lucida on Zeiss microscope, from preparations stained with Sudan III-haematoxylin. In all cases, magnification is  $800\times$ .

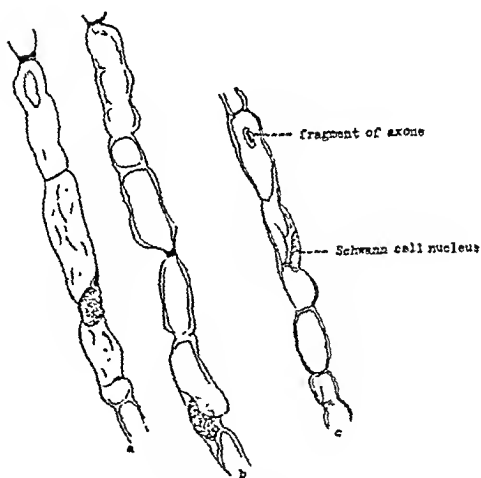


FIG. 3. FOSC 1. Left sciatic cut 13 days previously.  $T = 18^{\circ}$ – $20^{\circ}\text{C}$ . *a* is 4 cms. from cut end; *b* is 5.3 mm. from *a* on the same fiber; *c* is intermediate between the two. It is usually held that the smaller the myelin segments, the more advanced the degeneration. This, then, could not be centrifugal progressive degeneration. Essentially the same condition was found 8.4 to 9 mm. from *a*.

A nerve degenerating at 18°–20°C. for thirteen days, still conducting sufficiently to cause muscle contraction, was examined for a cm. length. 4 cms. from the cut end, as Fig. 3 shows, there is still relative uniformity of degeneration, at a stage much more advanced than that shown in Fig. 2. In no case were fibers found with great fragmentation at one end, and normal appearing segments at the other. It should be emphasized that isolated fields containing different fibers give erroneous impressions unless sufficiently large numbers of fibers are counted. Heinbecker, Bishop, and O'Leary (1932), who made adequate counts, pointed out (p. 7): "... the occurrence of undoubted degenerative changes in a variable number of fibers observed in histologic sections is not a true index of the state of the nerve as a whole." This was not considered by Parker and Paine (1934) in their work on the lateral line nerves. The necessity for observing large numbers of fibers on a statistical basis was obviated in this study by teasing fibers and groups of fibers so that they could be followed for comparatively long distances. 300–400 fibers were teased from the frog nerves cut 12–16 days previously, and in no case was progressive degeneration observed: on the contrary, similar degenerative changes were found at widely separated regions of the same fiber.

#### DISCUSSION

Loss of indirect excitability might be due to a failure at the end plates or to breaks in the functional continuity of the motor axones. If the motor end plates degenerate prematurely so that even when axones still conduct, block occurs at the neuro-myel junction (Tello, 1907; Titeca, 1935; Holobut and Jalowy, 1936), then no conclusive statements regarding progressive degeneration in nerve can be drawn from muscle twitch experiments. It would be impossible to obtain twitches from stimulation of one nerve region and not from others, as claimed by Parker. If, however, the motor axones degenerate first, or simultaneously with the end plates, then the simultaneous loss of indirect excitability along the nerve trunk is positive evidence of a non-progressive degeneration. Only if axones degenerate first and progressively as described by Bethe (slow progression from the cut end, starting immediately after the injury) or by Parker (progressive degeneration found only between 12 and 16 days after injury) could a centrifugal loss of indirect excitability result. Since both requirements are refuted by the facts presented, this may be excluded.

It is clear that a definitive answer to the question of the progress of degeneration in nerve must rest on analyses within the nerve itself to exclude the end-plate complication. Action potential studies, of nerve function, have been unanimously against progressive degeneration; and histological ones, of nerve structure, predominantly so.

One hypothesis as to degeneration posits that some chemical substance, arising in or near the nucleus, is transmitted to the rest of the nerve fiber, and that it is the lack of this compound (or compounds) which causes degeneration. The "chemical theory" is compatible with either simultaneous or pro-

gressive degeneration, depending on the subsidiary assumptions made; and although Parker and Paine (1934) used it as support for their observation of progressive degeneration in catfish nerve, Bethe (1903), long an adherent of the progressive degeneration theory, rejected the chemical theory for, to his mind, it left no alternative but simultaneous degeneration. This theory was first proposed by Goldscheider in 1894. It has recently been supported and amplified, as against a theory requiring constant passage of trophic impulses, by Cook and Gerard (1931) and Gerard (1932), who observed that increased activity of severed mammalian nerve caused a more rapid degeneration; and similar results were obtained on frog nerve *in vitro* by Abrams and Gerard (1933). Torrey's (1935) observations on the temperature coefficient of degeneration in frog nerve also supports such an hypothesis. Plausible means for the sufficiently rapid spread of chemicals along nerve fibers have been suggested (Gerard, 1932; Abrams and Gerard, 1933; Parker and Paine, 1934). The nature of the essential substance has been speculated about (Marinesco, 1930, and others), and Minea (1932) has reported a slowing of degenerative processes in rabbit nerve by injections of lecithin and antilipase sera. Certainly the axone, with its independent blood supply, furnishes an admirable test object for studying substitutes for the nuclear influence.

#### SUMMARY

The cut left sciatic nerves of leopard and wood frogs kept at 18°-20°C. lose the capacity to transmit impulses to their attached gastrocnemii 13-14 days after section. This loss, measured by muscle twitch height, occurs simultaneously throughout the length of the peripheral stump. At 12°-15°, the physiological degeneration is not complete until the seventeenth day after the cut.

Action potentials from these nerves decline and disappear simultaneously throughout the length of the nerve as degeneration progresses.

Histological examination of teased out fibers of degenerating nerves with a modified Sudan III-haematoxylin stain, shows no linearly progressive myelin degeneration.

Discrepant findings by others can be accounted for in terms of the use of stimuli which were inadequate in view of the presence of branches and of the irregular distribution of motor fibers in the frog sciatic, and to failure to eliminate the area of traumatic degeneration at the cut end of the nerve.

These results have been confirmed in rats, where the loss of indirect excitability occurs from 50-70 hours after section. This conforms with the results of Heinbecker, Bishop, and O'Leary on various nerves in cats and monkeys.

I wish to thank Dr. R. W. Gerard for his invaluable suggestions and criticisms. Thanks are also due Mr. F. Offner for his gracious assistance with the electrical apparatus.

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# AN OSCILLOGRAPHIC STUDY OF THE CEREBELLO-CEREBRAL RELATIONSHIPS\*†

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## I. INTRODUCTION

RECENTLY the relationship of the cerebellum to the activity of the cerebral cortex has been stressed by experimental and clinical (Walshe, 8) studies. Rossi (6) (confirmed by Bremer, 2) showed that simultaneous stimulation of a lateral lobe of the cerebellum rendered a previously infraliminal stimulus capable of producing a motor response from the contralateral cerebral cortex. Fulton and his associates (1, 5) have shown experimentally the importance of the cortex in the genesis of the cerebellar disturbances. Anatomical studies have indicated the structural basis for these physiological phenomena by demonstrating that the main efferent connection of the cerebellum of primates is with the contralateral motor and premotor areas through thalamic relays. In view of these advances, it seemed probable that, if the cerebellum played an active rôle in the functioning of the cerebral cortex, changes should occur in the action potentials of the motor areas with cerebellar stimulation.

## II. METHODS OF INVESTIGATION

The isolated encephalon of the cat, a preparation introduced by Bremer (3), has been used for all the experimental procedures. The preparation is simply made, and once established, no further anaesthetic is necessary. Under ether anaesthesia the posterior neck muscles are scraped from their insertions on the occipital bone to expose the arch of the atlas and the foramen magnum. The intervertebral ligaments and dura between these are incised, bringing into view the lower part of the medulla. With a blunt spatula the exposed medulla is completely transected at approximately the obex. At the time of transection the animal should be deeply anaesthetized to prevent undue shock. Artificial respiration is maintained for the remainder of the operation. A small dose of ephedrine (0.01 gm. per kilo) increases the blood pressure, depressed as the result of lowered vasoconstrictor tone, and insures a good encephalic circulation. The cerebellum, on one or both sides, and the cerebral cortex are exposed in the usual manner and cortical potentials led off by one or two pairs of electrodes (5-6 mm. apart) placed indirectly upon the cortex and recorded after amplification by the Matthews or Dubois oscillograph. Small electrodes connected to the secondary coil of an inductorium, the primary of which is in series with a two volt battery and a key, are used for

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bipolar stimulation of the cerebellar cortex. The frequency of stimulation varies from 12 to 25 break shocks per second. The strength of excitation is generally about that necessary to obtain a motor response from stimulation of the cerebral cortex. Both the stimulating and receiving electrodes are firmly attached to the calvarium by wax, so that slight movements of the head do not introduce an artefact. All experiments were carried out in a completely shielded room; the inductorium was separately shielded.

### III. EXPERIMENTAL RESULTS

Faradic stimulation of the cerebellum, especially the cerebellar hemispheres, produces changes in the cortical potentials obtained from the motor areas and to a lesser extent from the parietal and temporal regions. These alterations consist of an increased frequency and amplitude of the cortical waves. Usually the change is striking and not at all to be confused with the unavoidable artefact introduced by spread of potential from the stimulating electrodes. The response usually is initiated by a wave which at times so closely follows the artefact that they seem to be almost synchronous, but which reaches its acme much slower than the spike of the artefact. It is of greater amplitude than the normal cortical waves. Usually smaller secondary waves are present. Their frequency is definitely greater than that of the normal cortical activity, the increase varying between 25-50 per cent. These effects appear immediately without a delay. In some cases they may augment during the first second of stimulation. Following the stimulation the large waves cease immediately, but the cortical activity may not regain its normal rhythm for a half or one second. During this interval the waves are of greater frequency and smaller amplitude than normal. Another feature may superimpose upon this response. During spontaneous sleep, which was frequently the state of the animal, the cortical rhythm is punctuated every few seconds by spontaneous bursts of activity. Cerebellar stimulation may augment the number, intensity and duration of such bursts (Fig. 2 A). Auditory stimuli give rise to similar changes of the cortical potentials led from the temporal lobe (Bremer, 4).

It has not been possible to facilitate the response by repeated stimulation of the cerebellar cortex at small intervals, nor has it been possible to tire or fatigue the response similarly.

These responses to cerebellar excitation may be readily obtained from the motor cortex surrounding the cruciate sulcus and extending posteriorly along the midline. In only three of twenty-one experiments was cerebellar stimulation ineffective, probably due to the poor general condition of the animal. Responses may be obtained to a lesser degree from the parietal and temporal\* cortex. Although less distinct and requiring a slightly greater strength of stimulation, such responses present the same characteristics as those obtained from the motor area. Cerebellar stimulation caused no alteration in the po-

\* The differences in the resting or normal cortical rhythms of the frontal, parietal and temporal cortex, as pointed out by Kornmüller have been constantly a striking feature.

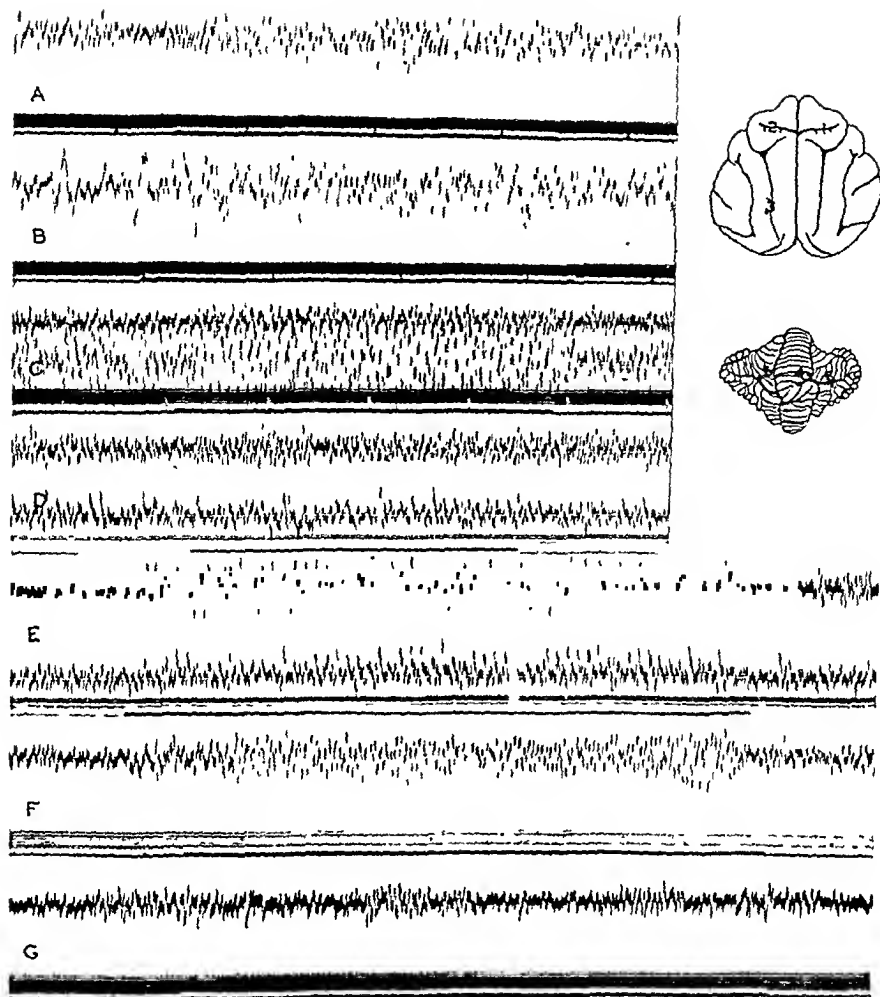


FIG. 1. A and B (cat No. 10) Stimulation of right cerebellar hemisphere with secondary coil of the inductorium at 22.5 cm.

A. Leads from the left cruciate sulcus (point 2).

B. Leads from left parietal cortex (point 3).

C, D and E. (cat No. 11) lead I (upper) from right cruciate sulcus; lead II from left cruciate (points 1, and 2).

C. Stimulation of the right cerebellar hemisphere along the intercrural fissure (secondary coil at 23 cm.).

D. Stimulation of same point as C, but right superior cerebellar peduncle sectioned 15 min. previously (secondary coil at 23 cm.).

E. Stimulation of left cerebellar hemisphere along the intercrural fissure (secondary coil at 25 cm.).

F and G. (cat No. 5) Cortical lead from the left cruciate sulcus (point 2).

F. Stimulation of the lateral portion of the right inferior ansiform lobe (point 6).

G. Stimulation of the right inferior ansiform lobe 3 mm. medial to the point stimulated in A and near the vermis. Secondary coil of the inductorium was set at 26 cm. for F and G, which were taken within 1 min. of each other. (Cont. on p. 19.)

tentials led from the cortex of the occipital lobe other than the spike produced by the spread from the exciting electrodes in the only two cases so studied.

The changes may be markedly diminished or abolished by local application of novocaine or ice to the cerebellar cortex. Under such circumstances although the cortical activity remains normal, cerebellar excitation produces very slight, if any, alteration in the cortical rhythm. The influence of the artefact alone may thus be seen (Fig. 2 B). If the effect of these depressing

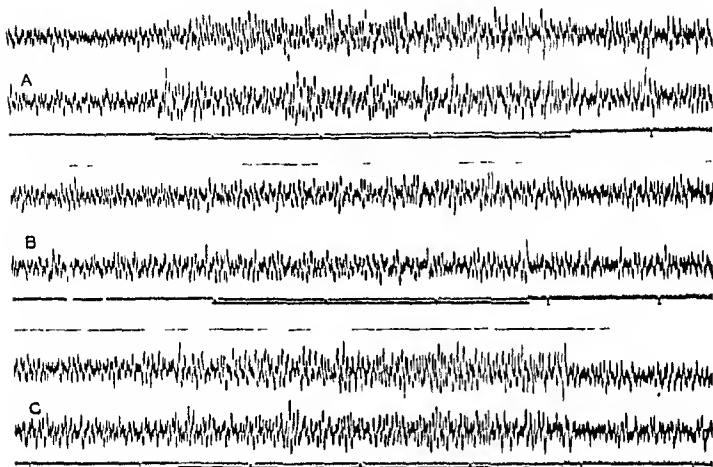


FIG. 2. (cat No. 16) Lead I (upper) from just inferior to the tip of the left cruciate sulcus, and lead II from slightly inferior and posterior to the left coronal sulcus. Stimulation of the right inferior ansiform lobe with the secondary coil of the inductorium at 24 cm.

A. Control record to show the response to stimulation.

B. Record taken after five minutes application of ice to the cerebellar cortex.

C. Record taken eight minutes later to show the response again.

agents is allowed to pass off, stimulation of the cerebellum once more produces marked alterations in the cortical activity (Fig. 2). Following application of 2 per cent novocaine to the cerebellar cortex, strengths of stimulation formerly producing a good response are no longer effective, but stronger excitation may give rise to changes in the cortical potentials. This is not un-

In all records the sensibility of the oscillograph was 20 mm. for 100 uv. The time marker signalled 1 sec. intervals. In a few of the earlier experiments owing to mechanical difficulties, there was a slight delay between the signalling of the closure of the secondary circuit of the inductorium and the onset of excitation. This gives the false impression of a latent period (Fig. 1 F).



expected for such strong stimuli must reach the deep cerebellar nuclei which are not affected by the local anaesthetic.

Abolition of the cortical activity by asphyxiation, readily carried out in the isolated encephalon by discontinuing artificial respiration, prevents a response to cerebellar stimulation. The only effect of such excitation is a series of spikes produced by the spread of potentials from the stimulating electrodes. If artificial respiration is resumed the activity of the cerebral cortex

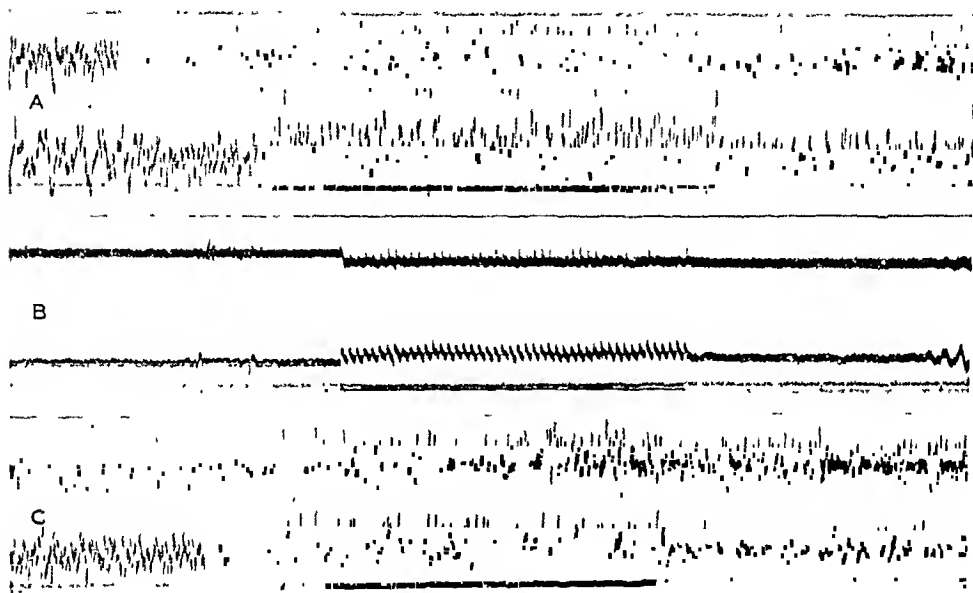


FIG. 3. (cat No. 18) Lead I (upper) from the inferior part of the left cruciate sulcus, lead II from the cortex immediately superior and posterior to the coronal sulcus on the same side. Excitation of the inferior ansiform lobe (right) with the secondary coil of the inductorium at 23 cm.

A. Control record to show the response from these two leads.

B. Record after three minutes asphyxia.

C. Record taken three minutes after B, and two minutes after the resumption of artificial respiration.

rapidly returns and cerebellar stimulation will again produce a response (Fig. 3).

The application of strychnine to the cerebellar cortex has failed in two instances to produce alterations in the cortical activity.

Section of the superior cerebellar peduncle in the two experiments studied has abolished the response obtained from stimulation of the same side of the cerebellum without altering the effect of exciting the opposite hemisphere. In these cases leads were taken simultaneously from both motor areas along the cruciate sulcus. The effect of cerebellar stimulation is thus shown to be not strictly unilateral, a weak response being present in the ipsilateral motor cortex (Fig. 1, C, D, and E).

The response varies with the point of the cerebellar cortex stimulated. Excitation of the vermis does not give any response at times, and at best, it does not give rise to nearly so pronounced changes in the cortical activity as excitation of the cerebellar hemispheres. Within the latter are optimal places for producing a response in any particular point of the cerebral cortex. However, the results of such studies have not been sufficiently constant to warrant a statement regarding cerebellar localization. In general better responses are obtained when the exciting electrodes span the small sulcus between the superior and inferior ansiform lobes (*fissura intercruralis*) than when either the superior or inferior lobe is stimulated alone.

The method of preparing the animal does not allow coincidental observations on the effect of cerebellar stimulation on the posture of the extremities. Changes in the cortical potentials may occur quite independent of eye movements, which are readily elicited from the anterior part of the cerebellum in this preparation.

#### IV. DISCUSSION

The increase in the cortical activity subsequent to excitation of the cerebellar hemispheres probably represents a normal function of the cerebellum. Certainly the fact that the changes are abolished when the activity of the cerebellum is arrested by novocainization, or the local application of ice, or its main efferent pathway interrupted by section of the superior cerebellar peduncle is ample evidence that they do not represent artefacts introduced by the potentials of the stimulating electrodes. Because the cortical activity does not appear to be altered by removal of the cerebellar influence by any of these methods it may be assumed that in the cat the cerebellum, while physiologically at rest, does not add a perceptible factor to the cortical rhythm. It is possible that this may be correlated with the fact that hypotonia is not a prominent sign following removal of the cerebellum in this animal. The fact that the cerebellum is able to increase the activity of the motor areas leads to the supposition that the former is exerting a stimulating influence on the cerebral cortex. There is, however, no reason to suppose that this influence is sufficient to produce the specific response of the motor cortex, rather it would appear merely to sensitize the cortex so that it might be activated by a minimal stimulus. In other words it serves to lower the threshold of excitation of the cerebral cortex. Thus one would expect that subthreshold stimuli would produce motor responses when the cerebellum was simultaneously stimulated. This Rossi (6) has shown is precisely what happens.

The fact that the effect is most pronounced in the motor cortex is not surprising in view of previous anatomical (Walker, 7) and physiological (Aring and Fulton, 1) studies. It is possible that the response may be entirely confined to the motor cortex in animals in which the cerebral cytoarchitecture is better differentiated, such as in the monkey, ape and man.

It is probable that both the cerebellar cortex and deep nuclei of the cerebellum take part in the production of this stimulating influence, for although

local application of novocaine abolishes the effect of weak stimuli, stronger ones produce a response. It is likely that this latter effect is due to excitation of the deep cerebellar nuclei. The efferent pathway is by way of the superior cerebellar peduncle to the thalamus. Another neurone then projects to the motor areas of the cerebral cortex. This pathway has been clearly demonstrated anatomically in cat, monkey and anthropoid ape.

That the effect is mainly obtained from stimulation of the neocerebellar parts is not unexpected in view of the anatomical, physiological and clinical evidence that neocerebellar function is largely dependent upon the integrity of the cerebral cortex. Comparative anatomy has taught that the cerebellar hemispheres develop *pari passu* with the elaboration of the cerebral cortex. Fulton, Liddell and Rioch (5) and Aring and Fulton (1) have shown that cerebellar tremor, essentially a sign of neocerebellar dysfunction is greatly diminished or absent following ablation of the motor cortex.

The neocerebellum is not entirely concerned with the cerebral cortex. Undoubtedly it plays an important rôle in association with the parvicellular part of the red nucleus and the rubroreticular tracts. In ascending phylogeny, however, the neocerebellum is more and more functionally related to the cerebral cortex, especially to the motor and premotor areas.

The significance of this cerebellocerebral relationship is to be found in an analysis of the disturbances resulting from lesions of the cerebellum. Bremer in a recent excellent survey of the subject concludes as follows (2, p. 126): "L'analyse du syndrome de déficit néo-cérébelleux et la considération des connexions cérébello-cérébrales nous amène donc à formuler l'hypothèse que les trois éléments de ce syndrome, l'asthénie volontaire, l'hypotonie musculaire et les anomalies des temps de réaction volontaire, sont l'expression d'une seule et même perturbation fondamentale: le défaut de tonus, l'asthénie, des mécanismes moteurs cortico-bulbaires et cortico-spinaux privés d'une action dynamogénique cérébelleuse." Such a cerebellar action is well confirmed by the present investigation.

The absence of this cerebellar dynamic influence increases the threshold of the cerebral cortex, and in higher primates at the same time releases the peripheral musculature from that slight cortical stimulation which is probably the basis of normal tone. In these circumstances the cerebral cortex must be set into action by an abnormally strong excitation, one which on account of its abnormal strength is apt to produce a response of too great or too little intensity. The lack of tone of the peripheral musculature introduces another disturbing factor. When this is summated by the same abnormal reaction of the antagonists which normally modulate the activity of the agonists, a physiological basis for the ataxia, tremor and dysmetria seen in cerebellar lesions is apparent.

## V. SUMMARY

1. Excitation of the cerebellar hemispheres produces a marked increase in the amplitude and frequency of the cortical action potentials from the motor areas of the cat.

2. Section of the superior cerebellar peduncle abolishes the response of the contralateral motor cortex but a slight change in the potentials of the ipsilateral motor cortex may still be elicited.

3 From these experiments it is concluded that the cerebellum especially the neocerebellum exerts a stimulating influence upon the cerebral cortex, which may be the mechanism through which the cerebellum normally maintains a coordinating influence upon volitional movement.

The generous kindness and encouraging criticisms of Professor Fr Bremer, under whose direction this work has been carried out, have been greatly appreciated I would also like to thank M Tirabassi for technical assistance with this research

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# HUMAN BRAIN POTENTIALS DURING THE ONSET OF SLEEP

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WHEN A person goes to sleep, the pattern of his brain potentials alters systematically. Five clearly defined stages have already been described (Loomis, Harvey, and Hobart, 1937) as follows:

- A—*interrupted alpha*: the normal waking 10-per-second rhythm dominates the pattern
- B—*low voltage*: the alpha rhythm is lost
- C—*spindles*: short groups ("spindles") of 14-per-second waves appear and also random "delta" waves 0.2 second or more in length
- D—*spindles plus random*: both types of wave increase in voltage and the delta waves become longer
- E—*random*: the 14-per-second waves become inconspicuous, but delta waves continue to increase in voltage and wavelength

We have now investigated the finer details of the *A* and *B* stages, and are able to relate alterations of the electrical pattern of the brain to signals given by the subject which are based upon changes in his state of consciousness. Such a correlation is of great interest from the point of view of psychophysiology, for it unites a subjective with an objective aspect of brain function.

## METHOD

The experiments to be described were carried out in the Loomis Laboratory. We employed the amplifiers, the ink-writing oscillographs, the automatic recording drum and accessory apparatus, which have been in use in this laboratory for some time (Loomis, Harvey, and Hobart, 1936). In addition we employed the portable two-channel ink-writing electroencephalograph and associated amplifiers which are in routine use in the Department of Physiology of the Harvard Medical School. These were designed and constructed by Mr. A. M. Grass.† The two sets of instruments on direct comparison proved to be almost identical in their characteristics. The only exception is the electrical filters. The Loomis filters are quite sharply tuned and select one frequency rather specifically from the medley of brain activity. The Harvard filters, on the other hand, are much more broadly tuned‡ and can be legitimately compared to combinations of high-pass and low-pass filters, leaving a band of a third of an octave or more which is passed with relatively

\* Following the suggestion by Walter (1936) we employ "delta" as a generic term to designate brain-potential waves whose wavelength is 0.2 second or longer. They may or may not be rhythmic in sequence.

† The work of the Harvard group has been materially aided by a grant from the Josiah Macy, Jr. Foundation.

‡ The higher the frequency to which one of these filters is tuned, the sharper is the tuning. The sharpness may be expressed as the ratio of the frequency at which the amplitude of a sine wave is  $\frac{1}{2}$  what it is at the center of the band to the frequency of the center of the band. For 3 per second this ratio is 2.7; for 10 per second, 1.4; and for 14 per second, 1.3.

little distortion. Each type of filter has proved of particular value for particular purposes.

Two signal pens connected in parallel write upon the drum and the tape, respectively. They are connected to a push-button operated by the subject, or to a mercury contact switch driven pneumatically by a rubber bulb held by the subject. (The rubber bulb was introduced to eliminate a rather troublesome electrical artifact which emanated from the push-button and its grounded shield.)

Small metal electrodes were attached in standard positions on the heads of the subjects as follows: (1) Vertex; in the midline directly on the top of the head on a frontal plane through the two auditory meatuses. This point is over or near the sensorimotor area of the legs. (2) Occiput; in the midline about 2 cm. above the inion. This point is over the visual area of the brain. (3) and (4) The right and left mastoid processes or the right and left ear lobes. Points 3 and 4 were used either singly or connected in parallel, as reference electrodes common to all of the recording circuits. We shall speak of electrical activity at the vertex or occiput when we mean, strictly, the electrical potential appearing between vertex or occiput and these ear electrodes. The degree of unlikeness which appears between simultaneous occiput and vertex records shows that it is safe to assume that not more than 10 per cent of the electrical activity is due to potential changes of the ear electrodes, except perhaps in the stage of deep sleep.

Two types of electrode were used in different experiments—(1) a small flat coil of silver wire and (2) a flat drop of solder in which the end of a copper lead-off wire is imbedded. No systematic difference between the results obtained with these two types of electrode could be determined. Much more important than the type of electrode was the state of the subject's skin and the firmness of mechanical contact. Electrical contact was made with Sanborn Electrode Paste and the electrodes were held in place by collodion. It is not difficult to obtain satisfactory electrical and mechanical contact with the scalp without even cutting a hair.

The subject lay comfortably on a bed in a darkened room. A steady noise from an electric fan provided a constant auditory background and masked accidental noises from other parts of the laboratory. The subject was instructed to settle down for an afternoon nap or for the night's sleep, as the case might be, but to signal by squeezing the bulb once whenever he realized that he had just "drifted or floated off" for a moment. The subjective aspect of this "drifting" or "floating" on the borderline of sleep varies with different individuals and will be described in detail below. The subject was also instructed to signal twice if he felt that he had just awakened from "real sleep." Most of our subjects drew a definite distinction between these two experiences. If the subject was still awake after he had given ten or fifteen signals, the experimenter entered the room and obtained from him a description of the subjective experiences indicated by the signals. If he fell asleep as deeply as the C stage, it was sometimes necessary to awaken him deliberately.

## RESULTS

We have carried out twenty-eight experiments on fourteen different subjects. Three experiments were inconclusive as to any psychophysiological correlation, as the subjects gave no signals. In one case the subject fell immediately asleep without "drifting," and in the other two the subjects were unable to relax sufficiently to reach the "drifting" stage. Five other experiments were qualitatively positive, but are not considered in detail because of technical differences or inadequacies which make it impossible to compare them in detail with the main series. In the remaining twenty experiments satisfactory records and signals from eleven subjects were obtained. For purposes of exposition, we shall disregard for the moment the signals from the subject and first describe the typical onset of sleep in terms of electrical activity of the brain.

*The onset of sleep.* We can distinguish several fairly well-defined steps in the approach and onset of sleep. These steps are not to be confused with the stages A, B, C, etc., of Loomis, Harvey, and Hobart, but represent a more refined analysis of stages A and B.

As a subject "settles down" his alpha waves may first increase slightly in voltage and regularity, but in subjects who have a steady alpha rhythm, a modulation of the alpha waves soon appears, i.e., the alpha waves systematically increase and decrease in voltage. The period of this modulation is several seconds and is sometimes quite rhythmical. The maximal amplitude of the alpha waves also tends to be reduced. Many individuals show a similar modulation of the alpha waves even when fully awake, and in such an individual the trains of alpha waves become shorter and the voltage lower as he becomes drowsy.

The second step is complete interruption of the alpha rhythm for periods of 1 to 5 seconds. Sometimes the alpha activity does not disappear entirely during these gaps, but the waves become small and irregular both in shape and frequency (Fig. 1B and C). A sharply tuned filter fails to respond to them.

The third step is that the interruptions of alpha activity become longer, although at the end of each gap the alpha waves return quite suddenly, usually with their normal maximal amplitude. At this stage an increase in voltage of the longer, random, delta waves can first be clearly identified. The delta waves appear during the gaps in alpha activity. Most individuals show some slow waves of low voltage at all times as a slight irregularity of the baseline, but in the stage in question slow waves appear singly or in groups of three or four, sometimes quite rhythmically at a frequency of 4 or 5 a second, with a voltage of approximately 50 microvolts (Fig. 1D). The delta waves tend to be larger and more easily identified at the vertex than at the occiput. The changes in alpha activity, on the other hand, are most clearly discerned in the occipital record.

Some individuals have little or no alpha activity in the waking state, but have instead many shorter, sharper waves of 50 to 60 msec. in wavelength which appear irregularly or in brief trains. When they are regular enough to

constitute a definite frequency it is usually 17 to 20 per second (Fig. 2B). These waves are clearly quicker than alpha waves and they do not disappear when the eyes are opened, yet they are slower than the waves which generally have been designated as "beta" waves, namely, those with frequencies above 20 per second (Berger, 1929, 1930, 1934). In their general characteristics they seem more nearly akin to beta than to alpha waves. They are more prominent at the vertex than at the occiput. A generic term for these waves would be convenient, but it seems wiser to defer assigning a Greek letter or other

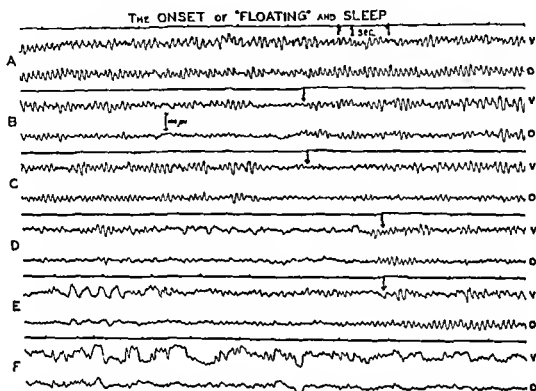


FIG 1 Six sections from the record of a subject going to sleep and signaling "floating" The upper line of each record shows potential changes at the vertex (V), the lower, at the occiput (O), with reference to the ears Upward deflection means O or V negative to ears Time scale and amplification are constant throughout as shown in the figure A Normal record of the subject awake B, C, D, E "Floating" with signals from the subject on rousing Drowsiness is increasing throughout this series Note in B that the alpha waves disappear at the occiput before they disappear at the vertex Note that in C the subject's signal precedes the return of alpha waves F Real sleep, entering the C stage, with waves at 14-per second and 12-per second in addition to large delta waves The largest delta waves appear square-topped because the limit of the linear range of the recording system has been reached The actual voltage of these waves is at least 150 microvolts

specific designation to them until more is learned of their significance and relationships In this paper we shall refer to them as "quick" waves, and reserve "beta" for frequencies above 20 per second and wavelengths of 50 msec. and shorter.

Three individuals in our series, whose waking records are dominated by these quick waves, show the usual increase in delta waves with the onset of sleep. As drowsiness increases, there is a general reduction in voltage and usually also in the average frequency of the quick waves. The quick waves do not cease entirely, and, inasmuch as they are often quite irregular even in



the waking state, there is no abrupt loss of regularity such as we find in the typical alpha waves.

The fourth step in the onset of sleep shows an increase in the wavelength of the delta waves which appear during the gaps of alpha activity. Alpha waves, when they appear at all, show a slower frequency than the individual's normal waking rate (Fig. 2C). The slowing usually amounts to 10 per cent, and may be as much as 20 per cent. The slowing is not uniform, however, for immediately following a gap, when the waves first return, they are accelerated by as much as 10 per cent above the waking frequency and then progressively slow down to 9 or  $8\frac{1}{2}$  per second before the next interruption. The temporary acceleration is particularly evident if the subject has given a signal and it is very similar to the acceleration which often occurs when the subject opens his eyes for a few seconds and then closes them again. *The slowing of the alpha rhythm below its normal frequency is a characteristic phenomenon associated with the approach of real sleep*, although it may not be very evident if an individual goes directly into deep sleep without lingering in the intermediate "floating" stage.

The fifth step is characterized by the complete loss of alpha waves and by the appearance of delta waves of 150 microvolts or more (Fig. 1F). If the delta waves are rhythmic, as is frequently the case, the most characteristic frequency is 4 per second or a little slower. We shall see later from the subjective reports of the subjects that this stage should be regarded as probably real sleep.

The next stage, which is certainly sleep, corresponds to the C stage of the original classification (Loomis, Harvey, and Hobart, 1937) and is identified by the appearance of characteristic brief trains ("spindles") of waves at 14 per second and 50 microvolts or more in voltage (Figs. 1F, 2F and 2G). In this stage there is a still further increase in the average voltage of the delta waves and also an increase in their average wavelength.

If we compare the preceding description of the alpha waves with the original classification of the A, B, and C stages of sleep, it appears that the A and B stages alternate with one another for a time as the subject goes to sleep. This description is incomplete, however, for, although there is a fluctuation between alpha activity and absence of alpha activity (which we shall find is correlated with temporary subjective changes in the state of consciousness of the subject), there can nevertheless be traced a general trend underlying these briefer fluctuations. This trend appears as a lengthening of the periods of absence of alpha activity, as a progressive slowing of the alpha rhythm, and also as an increase in voltage and average wavelength of the delta waves when they appear. The general trend is associated with increasing drowsiness of the subject. On this general trend is superimposed a series of fluctuations of some other factor, which is expressed by the intermittent outbursts of alpha activity.

As a rule, alpha activity and delta activity are inversely related, that is, delta activity tends to appear only when alpha activity is suppressed. This is

true in general, but it is important to note that the rule is not invariable. Particularly in the very early stages, before the alpha rhythm is significantly slowed, the alpha waves may disappear for a few seconds without any measurable increase in delta activity. Furthermore, the alpha waves may disappear

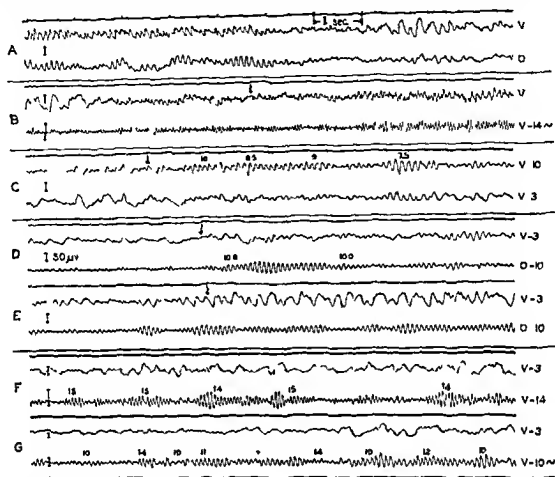


FIG 2 Brain potentials from vertex (V) or occiput (O) referred to the ears Upward deflection = scalp negative Broadly tuned filters used in all except A and upper line of B. Frequency of filters shown by numerals at extreme right Voltage calibrations at left, 50  $\mu$ v in all cases When tuned filter is used calibration refers to peak-to-peak voltage of a sine wave of frequency matching the tuning of the filter

A Unfiltered, showing unusually prompt appearance of delta waves in a brief "float" (or nap?)

B End of a "float," with subject's signal at arrow showing return of "quick" 18-per-second waves in a subject with very few alpha waves Lower line shows the same potentials taken simultaneously through a 14-per-second filter. The frequency of the waves is approximately 18 per second

C Return of alpha waves after a "float," showing variability and slowing of alpha rhythm in the very drowsy state Alpha frequency indicated on record The next "float" begins just after the sequence of 7.5 per second alpha waves Both records from the vertex Upper line filtered for alpha, lower line for delta

D and E Ends of two "floats" from the record of the same subject D The usual return of alpha waves shown in lower line, which is occipital record filtered for alphas E Shows unusual delta activity appearing at the vertex Alpha waves at the occiput continue unaffected by it This delta episode continued more than 30 seconds The subject signaled during the delta activity as shown, and behaved himself to be fully conscious throughout

F and G Records from the vertex of a single subject during sleep Upper line filtered for deltas, lower line for 14 per second and 10 per second F Typical 14 cycle "spindles" G Irregular slowing of 14 cycle waves, giving rapid shifts of frequency between 14 per second and 10 per second Frequency count shown on the record Note reduced amplification of G as compared with F Also in both cases lower line is taken at twice the sensitivity of the upper line

in one region—the occiput, for example—while they continue for a few seconds at the vertex, and *vice versa*. Still more important is the occasional appearance of fairly high delta waves running as a continuous background on which the alpha waves are superimposed, or a transient episode of great delta activity at the vertex while the alpha activity continues smoothly at the occiput. We may note immediately that, in the three such episodes of which we have clear records, the subject did not report sleep but believed himself to be conscious. In the case illustrated in Fig. 2E the subject reported unusual kinesthetic and somasthetic sensations, as if he were slightly dizzy and starting downward in a fast elevator. Whatever the significance of this report may be, it is clear that various parts of the brain do not always show simultaneous changes in the alpha and the delta waves.

*Correlation of Changes in the Electroencephalogram with the Signals from the Subject.* The subjects in these experiments signaled whenever they felt they had momentarily “floated” or “drifted” off or experienced any other clearly defined change in the state of consciousness. These signals correlated to a surprising degree with the alterations in the brain potentials (Figs. 1 and 2). The relation was clearest and most precise in those subjects whose standard waking record was largely occupied with alpha waves. Six of our subjects had such “high alpha” records, showing the alpha rhythm 70 per cent or more of the time. In 9 experiments these 6 subjects signaled “have floated” or “have slept” 165 times. All but 6 of these signals were preceded by definite depressions of the alpha waves which lasted from 1.5 to 30 or 40 seconds. The records showed only 39 equally clear depressions of alpha waves which were not signaled. One subject signaled correctly 20 consecutive depressions, and two others had consecutive runs of 10 or more. The minimal duration of a depression which was necessary for a subject to give his signal varied somewhat from one individual to another. One subject consistently signaled gaps as brief as 1.5 second, others required gaps of 4 or 5 seconds, but for each the minimal duration was quite consistent. The data of Table 1, based on two subjects, are broadly typical of the whole group, and also illustrate the characteristic prolongation of the “floats” as sleep approached.

The signal was usually given immediately after the return of alpha waves (Figs. 1B, D; 2C, D, E). The latency of the signal following the first re-appearance of alpha waves varied from zero to as much as 5 seconds, and is more or less characteristic of the particular subject. Occasionally the signal was given just *before* the alpha waves returned (Fig. 1C). This is a point of considerable theoretical interest, as it suggests that a subject may be able to realize that he has “floated” even when his alpha waves are still absent and that the waves may return because the subject rouses himself further by the act of signaling. In order to test this point it will be necessary to carry out similar experiments while obtaining records simultaneously from many parts of the brain, for the reappearance of alpha waves, like their disappearance, is not necessarily simultaneous at all points on the cortex. The latencies in Table 1 are all calculated on the basis of the return of alpha waves at the occiput, where these waves are usually most prominent.

In those cases in which the delta waves reached 150 microvolts and persisted for half a minute or more, the subject frequently signaled "real sleep" when he next awoke. Two subjects did not identify any intermediate stage between waking and real sleep, and almost all of the changes which occurred in their records involved the appearance of large delta waves for half a minute or more. Sometimes a subject who showed this type of change in the record would neglect to signal "real sleep" on waking, but state subsequently that he realized later that he had made a mistake and should have signaled "real sleep" rather than mere "floating." The situation suggests that the ability to discriminate between "floating" and sleep becomes relatively depressed when sleep actually occurs. Occasionally a period of one or two minutes of unquestionable sleep passed entirely unsignaled. This agrees with our expe-

TABLE 1

Subject	Signals	Average time between signals	Average duration of depression of alpha waves before signals	Average time from return of alpha waves to signal
A	1-5	16 9 sec	2 9 sec.	0 2 sec
	6-10	12 1 sec	4 1 sec	0 2 sec.
	11-15	17 8 sec	7 8 sec	0 4 sec
	16-20	20 5 sec	13 5 sec.	0 3 sec
	(sleep)			
B	1-3	30 2 sec	6 2 sec.	2 4 sec
	4-6	37 8 sec	10 4 sec	2 6 sec
	7-9	36 2 sec	22 7 sec	1 1 sec.
	(sleep)			

rience in other experiments in which such changes have appeared in the records and in which the subjects have denied having fallen asleep. Akin to this is the situation toward the end of an experiment when the subject is asleep most of the time and often fails to signal when alpha waves appear for a few seconds on the record. In this state the subject apparently does not arouse himself sufficiently to give the signal, and we have not included this part of the experiment in reckoning our scores. If we consider that even in the early "floating" stage the subject is in an extremely drowsy state, perhaps only semiconscious, it is surprising that our subjects actually attained an overall score of 75-per-cent accuracy of signaling depressions of alpha activity.

Failures to signal the changes perfectly occurred for several reasons besides extreme drowsiness. One reason was that on the first trial the subjects did not always sink deeply enough toward sleep. They did not attain the necessary condition for "floating," but, being anxious to cooperate, began signaling too soon, not waiting for the correct end-point. The failure was essentially the selection of the wrong subjective end-point. It is significant, however, that among all of the subjects who gave any signals at all only one failed to reach the proper end-point at one of his later trials; and even the one whose experiment we class as a failure was not entirely negative in his correlations toward the end of his second trial. According to his own statements, however, he was still shifting his end-point from time to time in an endeavor to find what we call the "floating" stage.

Occasionally the subject fluctuated very rapidly, according to his record, between a state of waking and a state of "floating," and under such conditions he frequently failed to signal all of the fluctuations. The period of such fluctuations was often as short as 5 seconds. Furthermore when the fluctuations are very rapid, the contrast between the sections of the record is often not great. The subjects expressed the greatest uncertainty concerning the subjective transitions on those very occasions when the record itself showed no sharp contrasts. Sometimes also there were very slow gradual transitions from one state to the other which apparently escaped the notice of the subject. It is significant that the very conditions which make judgment of end-points difficult on the record seemed to be correlated with a similar lack of clear definition and clear transition in the subject's own experience.

*The Subjective Experiences.* Two of the ten subjects in the successful experiments reported only "real sleep," and these two actually showed characteristic sleep patterns in 7 out of 12 alterations of pattern which were signaled. The first two alterations in each record were less clear than those which followed, but delta waves of at least 70 microvolts were visible in every case. The shortest period of delta activity was 10 seconds. These are more profound changes than our other subjects showed in their early "floats."

Our two youngest subjects (21 and 13 yrs.) gave no adequate description of their experiences. Their records passed quite rapidly into the characteristic sleeping pattern with only two and four intermediate "floats" (or naps?), respectively, but signals were given immediately after the alterations in every case.

The remaining six subjects who gave signals related to the changes in their potential patterns all agreed on two points—(1) that they would not call the early episodes "real sleep" but an intermediate stage, and (2) that during the episodes which they signaled there had been a depression of awareness or consciousness. The depression involved the awareness of immediate external stimuli (e.g., sounds, contact of the bed-clothes, etc.), or of self-consciousness, awareness of the experimental situation, etc. One of them compared the state to that of "nodding" or "dozing" during a lecture or sermon, and others agreed to the aptness of the comparison. Beyond these common points they gave the greatest variety of descriptions, such as:

(1) "These things are practically dreams, but I am awake enough to catch them." (99)\*

(2) "No dreams or visual fantasies. Mind a blank. Noises no longer noticed." (12)

(3) "Unexpected visual fantasies are my end-point." (98)

(4) "My thoughts wandered or floated unexpectedly." (15)

(5) "Drifting of thoughts. Definite kinesthetic sensation of being suddenly brought upright at the end." (95)

\* The figures in the parentheses following these descriptions are the "alpha indices" of the respective subjects, i.e., the percentage of the time occupied by alpha waves in his waking record under standard conditions (Davis and Davis, 1936; Saul, Davis, and Davis, in press.)

(6) "Pleasant sense of numbness, of dizziness, of being nothing at all." (72) These six spontaneous characterizations cover the senses of hearing, touch, equilibrium, and kinesthesia; and include thought, visual fantasy and dreams. They also include emphatic denials of dreams and visual fantasies.

We have no evidence relating dreams to specific changes in the record. The fantasies of the "floating" stage merge imperceptibly into dreams, and we have many unequivocal reports of dreams which must have occurred during the *B* stage, for the subjects never went beyond the *B* stage in those particular naps. One subject was awakened abruptly from the *C* stage by a knock on the door. He reported that he had just been dreaming and had awakened spontaneously, but had forgotten the content of the dream. Only 3 seconds elapsed from his last large "spindle" of 14-per-second waves (which preceded the knock) to his own signal indicating that he was awake, so that it seems quite safe to refer the dream to the *C* stage. Dreaming can therefore occur in both *B* and *C* stages. Concerning *D* and *E* we have as yet no evidence.

#### DISCUSSION AND INCIDENTAL OBSERVATIONS

In the reports of our subjects as to their subjective experience during the times when alpha waves were depressed in their records, no single sense modality is uniquely involved. We therefore cannot assume that the alpha waves are depressed in the "floating" stage because of *visual* activity in the form of fantasy, analogous to opening the eyes. In fact, "floating" seems rather to involve a depression of cortical activity, while opening the eyes and also those emotional states such as startle, "puzzlement," apprehension, etc., which suppress the alpha waves, are clearly forms of stimulation.

Inspection of the records leads to the conclusion that alpha activity may be reduced in two distinct ways. In one situation, as in "floating," the waves cease, simply *diminishing in voltage* to zero. They return again abruptly, then fade out once more, but, as they come and go, there is also, with the approach of real sleep, a general *slowing of the alpha rhythm* to 8 or even to 7 (cf. Durup and Fessard, 1936; Jasper, 1936). The slowing is most noticeable when the subject goes to sleep slowly with many "floats" in and out. Whenever the frequency falls to 7 or 6.5 per second the waves become irregular and disorganized and the subject passes off into another "float" or into real sleep. The behavior of the alpha waves resembles the slowing and disorganization of alpha waves in hypoglycemia described by Hoagland, Rubin, and Cameron (1936).

The 14-per-second waves which are so characteristic of sleep appear at about the stage when the last few recognizable alpha waves have been depressed to a frequency of approximately 7 per second. In a few instances in our records it appears that 7-per-second waves which are presumably slowed alpha waves have broken up into two groups which beat alternately with one another, thus generating a rather irregular 14-per-second frequency. The possibility of such an apparent doubling of frequency has been suggested in another connection by Rheinberger and Jasper (1937). This mechanism,

however, will not account for the genesis of the 14-per-second "spindles" in general, for the latter appear quite characteristically in the records of individuals who have no clearly marked alpha waves at any time. Also the 14-per-second waves are higher in voltage than the alpha waves at this stage of sleep.

The alpha waves are not the only ones which are progressively slowed with the onset of sleep. The quick (20-per-second) waves are similarly affected; in the individuals in whom the quick waves are prominent enough to be studied easily the groups of 14-per-second waves appear strongly when the average frequency of the quick waves has fallen to approximately 14 per second. This observation, although pointing to a genetic connection between the quick waves and the 14-per-second waves (cf. Jasper, 1937), offers no clue as to why the 14-per-second waves should reach a voltage higher than that exhibited by the quick waves at other frequencies. The frequency does not remain stable at 14 per second, but may oscillate between 14 and 10 per second or thereabouts (Fig. 2G). The "spindles" of 14-per-second waves have been identified because here seems to be a maximum of voltage and perhaps a somewhat greater stability of frequency in each train of waves.

Waves at approximately 10 per second may appear during sleep (cf. Blake and Gerard, 1937), but their frequency is seldom as regular as the waking alpha rhythm. Also a subject who has fallen asleep and lost his alpha waves for a time may show them again for a few seconds without signaling that he is awake, and they may be elicited regularly by stimuli which fail to arouse the sleeper. The pattern of brain potentials may change, and the subject may shift his position in bed, but when awakened may have no memory of the stimulus. The function of memory is certainly depressed. If the subject does give a signal in this state, its latency, with respect either to the stimulus or to the appearance of alpha waves, is unusually long—often many seconds, and giving the signal often involves great subjective effort. Whether or not we regard the subject as "asleep" under these conditions (when the alpha waves appear) is a question of definition which we shall leave open for the present.

One of our subjects always gave strong regular 10-per-second waves from vertex, occiput, and forehead nearly continuously while deeply asleep. There is no doubt as to the depth of sleep in this case. The 10-per-second waves appeared only in the C stage of 14-per-second waves. Frequencies of 10 and 14 per second often appeared simultaneously in the record. This subject gives such "alpha" waves *only* when soundly asleep. Her waking record is dominated by quick 20-per-second waves, and relatively few sharp irregular alpha waves appear. (The alpha index of this subject is 15.) It is a question whether or not her regular well-rounded 10-per-second waves in sleep represent the same cell-groups and mechanisms as the ordinary waking alpha rhythm. Her sleeping 10-per-second waves are strongest at the vertex instead of at the occiput, but this is also true for the waking alpha rhythm in about 2 per cent of our normal subjects. Obviously the test of opening the eyes could not be

tried in sleep! We believe that the sleeping 10-per-second waves in general are more closely akin to the 14-per-second waves of the spindles and to the "quick" 18- or 20-per-second waking waves than they are to the waking alpha rhythm. In sleep the 14-per-second and 10-per-second frequencies are not sharply differentiated. Many trains at 12 per second can be identified (See Fig. 2G). It is at 14 per second, however, that the highest voltages and greatest regularity are usually attained. In all subjects the sleeping 10-per-second waves, like the 14-per-second waves, are more prominent at vertex than at occiput, and they are equally strong in individuals with many and with few waking alpha waves.

Is "falling asleep" a unitary function or event? Our observations suggest that it is not. Different functions, such as sensory awareness, memory, self-consciousness, continuity of logical thought, latency of response to a stimulus and alterations in the pattern of brain potentials all go in parallel in a general way, but there are exceptions to every rule. Different functions may be depressed in different sequence and to different degrees in different subjects and on different occasions. Only the general progress of depression remains constant. We have pointed out that the changes in the pattern of brain potentials need not occur simultaneously in different parts of the brain. Only if we choose to define sleep in terms of response to a particular stimulus or of a particular change in the potential record from a particular area of the cortex—only then can a "moment of falling asleep" be precisely defined. Otherwise the problem is just as vague and difficult as that of determining the exact moment of death.

In terms of potential patterns the index which seems *most nearly* to reflect the "depth of sleep" is the frequency and voltage of the slow, random "delta" waves. Blake and Gerard (1937) have pointed out this general parallelism and it is implicit in the classification of stages of sleep cited in the opening paragraph of this paper. Our present observations show that the delta activity begins to increase both in voltage and in average wavelength at the stage of the earliest subjective "floating" or transition into sleep. The increase in voltage and wavelength appears to continue progressively as the physiological depression of the nervous system which we call sleep becomes deeper. It is probably no accident that most forms of mental disorder except the convulsive varieties have been reported as showing "slow waves" of one kind or another in those cases in which any difference from the normal could be detected (Berger, 1932, 1933; Gibbs, 1937; Walter, 1937; Jasper, 1937). We have confirmed this general relationship in a series of observations which will be reported in detail elsewhere.

The abruptness with which a subject's record can change from a high-alpha waking pattern to a "light sleep" record with clear delta waves (cf. Fig. 2A) raises an important practical point for clinical electroencephalography. Before we conclude that a low-alpha or a high-delta pattern is due to mental disorder, brain tumor, or other lesion of the brain, we must be certain that the patient was awake when the record was obtained and that he did not



momentarily "float off" in light sleep. Records must be carefully evaluated in terms of the state of the patient. Measurements of the amount of alpha activity are particularly subject to error from drowsiness, which may partially depress the alpha waves long before actual sleep occurs. Absence of drowsiness must be rigorously enforced as one of the necessary standard conditions for such measurements.

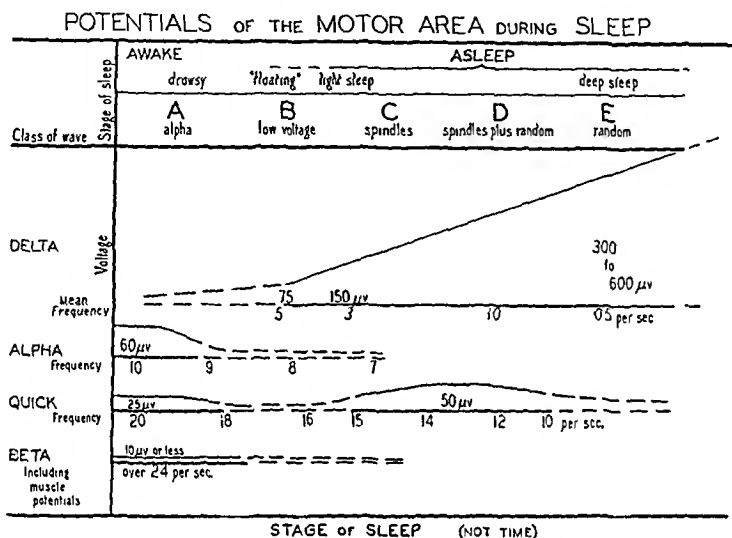


FIG. 3. In the upper line the stages of sleep are characterized by the subject's reports; in the next line, according to the classification of Loomis, Harvey, and Hobart (1937).

The classes of waves are defined by the values given for their frequencies. The delta waves sometimes have no clear frequency but appear as isolated waves, and strictly should be defined by wavelength rather than frequency. In sleep they tend to be fairly rhythmic.

The height of each curve above its own base-line indicates the most characteristic maximal voltage for that class of wave at the corresponding stage. Note that the voltage scale for delta is half that of the other classes.

Broken lines indicate that at the corresponding stage of sleep the frequency of the waves in question becomes irregular or that its appearance is very intermittent, or its identification uncertain.

The frequency of the alpha waves is the most definite and constant. The others vary from moment to moment by as much as 25 per cent. This may or may not indicate corresponding shifts in the "depth of sleep."

The chart describes the potentials from the motor area referred to the ears. The corresponding chart for the visual area is similar except for lower voltage of the delta and the "quick" classes of waves. Some individuals show very little alpha voltage, even when awake, particularly in the motor area.

The following chart (Fig. 3) summarizes graphically the typical behavior in sleep of the various components of the brain-potential pattern. It is to be regarded as tentative and highly schematic, since the various components are not necessarily as closely correlated with one another as this graphic representation implies, i.e., the dominant frequency of quick waves need not be exactly double the alpha frequency, although this is often the case. Broken lines signify variability of behavior or intermittent appearance of the corre-

sponding class of wave. It is important to note that the horizontal dimension does not represent time. A subject frequently shifts back and forth from one stage of sleep to another, sometimes quite rapidly and erratically.

## SUMMARY

Brain potentials were recorded from subjects while they were going to sleep. Alterations in the pattern were related to the state of consciousness of the subject by means of signals given spontaneously by the subjects (Fig. 1).

Subjects who have a well developed alpha (10 per second) rhythm when awake often showed repeated depressions or loss of alpha waves while going to sleep. Just after such a depression the subject typically signaled that he had "floated" or "drifted off" for a moment. Slow "delta" waves, 0.2 to 0.3 second in duration, usually appeared during the depression of alpha waves. Subjects who have few or no alpha waves showed a corresponding but less clearly marked depression of their "quick" (15 to 20 per second) waves, and the same appearance of "delta" waves.

Nine of our ten subjects gave signals which correlated clearly with alterations in their brain potential records. The "floating" state of consciousness always involves a loss of awareness for immediate external stimuli. Some subjects, but not all, also describe visual fantasies, kinesthetic sensations, interruptions of logical thought, etc.

"Real sleep" was regularly acknowledged when slow waves (recorded from the vertex) had reached 150  $\mu$ v and persisted for half a minute. The appearance of "spindles" of 14 per second waves is a sure sign of real sleep.

Dreams may occur in the low voltage, *B* stage and also in the 14 per-second, *C* stage

Alterations in the alpha and delta waves are not always simultaneous in different parts of the brain. We cannot define exactly the moment of going to sleep or the moment of awakening.

In the clinical study of brain potentials the drowsy state must be strictly avoided because of the similarity of the patterns of very early sleep to those described for many abnormal conditions.

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# THE BEHAVIOR OF CATS FOLLOWING BILATERAL REMOVAL OF THE ROSTRAL PORTION OF THE CEREBRAL HEMISPHERES\*

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TWO RECENT studies of the effects of bilateral removal of the frontal lobes of the cerebral cortex of the cat have been at considerable variance as to the symptoms obtained. Langworthy and Kolb ('35) have observed an exaggeration in motor activity in their animals and make no mention of a pronounced plasticity in the decorticate extensor hypertonus. Barris ('37), on the other hand, has reported a profound loss of motor initiative together with a hypertonus of an extremely plastic type suggestive of catalepsy and his comparison of this cataleptic condition with that investigated in this laboratory after brain stem lesions has led us to attempt to verify his observations. We have, therefore, subjected a series of cats to bilateral one stage removal of the frontal lobes.

## METHODS

The animals were operated under nembutal in the manner employed by Barris ('37). The skin was incised, the frontal sinuses opened, the nasofrontal ducts plugged with bone wax and the interior of the sinuses sponged with merthiolate. The anterior portion of the calvarium was then removed, the dura incised and all large available vessels were tied and sectioned. The cerebral hemispheres anterior to a plane in the region of the ansate sulci were removed on each side, hemorrhage was stopped, the subcutaneous tissue sutured and the skin closed with clips. Three animals were so active on the first and second postoperative days that they knocked the clips out of the anterior part of the medial longitudinal skin incision. These were killed immediately and in most of the remaining eight animals a transverse skin incision between the ears was employed and the animals were kept in a large cage during the first few postoperative days. Intraperitoneal injections of normal saline solution were administered daily until the animals ate.

The survival times of these eight animals were as follows: One cat suddenly became prostrate and died on the sixth postoperative day, possibly from embolism. One animal, in good health, widely opened its skin incision as a result of excessive activity during confinement for a test of temperature regulation on the sixth postoperative day, and was killed. Four to six weeks after operation, the remaining six animals were utilized in terminal experiments in which the excitability of the preoptic region and hypothalamus was tested. The results of the latter study, together with the information obtained regarding temperature regulation in these animals, will be reported in con-

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nection with other work. The following description is concerned with the animals' general symptomology.

### RESULTS

*Activity, postural defects, tonus.* In light of the loss of motor initiative which has been claimed for them, these animals exhibited a remarkable amount of activity usually from the first or second postoperative day onward. This was perhaps not abnormal since we have seen very restless normal cats which have been just as active. The activity was usually confined to an almost continuous walking about, but two of the animals trotted across the room on the third and fourth postoperative days. Though in motion most of the time when out of their cages for observation, the animals often stopped to look at other cats and seemed perfectly capable of inhibiting their activity. They would not at first turn aside to avoid obstacles, however, and with considerable difficulty would scramble over the rungs of a low stool in their path, or when walking across a table would walk over the edge. They showed a pronounced disposition to follow the observer duplicating every turn made by him.

At a time varying between the first and second postoperative week two of the animals lost this over-activity and disposition to follow and became about as quiet as the average laboratory cat. It was found at autopsy that these two animals suffered smaller cortical ablations than their fellows who continued to exhibit the above tendencies throughout their survival periods.

The loss of postural reactions, which the exacting study of Bard ('33) has shown to be dependent on the sensori-motor region involved in these ablations, made the animal's progress awkward during the first postoperative days, but improvement was rapid and subsequently postural defects were chiefly apparent when an animal was at rest, or starting or stopping motion, or when making a turn. These defects were usually manifest as a slipping of one or more of the limbs from under the body, forward, to the side or backward, or as a stepping on the dorsum of the foot. In two instances the fore limbs were crossed. Running or scrambling movements appeared when the animals were restrained from moving forward, the animals often becoming very excited.

It was quite impossible to pose the animals in any position.

An extensor hypertonus of the limbs was apparent in the standing posture and gait of two animals on the first postoperative day, but was usually present only when the limbs were freed of participation in standing or walking. It was seen best when the animal was suspended ventral side down either by the chin and tail or in a hammock, and then was marked and exhibited no plasticity. Usually in the course of the first postoperative week the animals became restless in the hammock, swaying the vertebral axis from side to side and making running movements of small amplitude. In most cases an extensor hypertonus of the limbs was apparent also when the animals were on their backs in a trough during the first two or three postoperative days, and some

of the animals would lie quietly in this position during the first postoperative week. Others, however, had to be restrained in the trough from the first postoperative day and righted themselves as soon as released, at first by a ventroflexion of the trunk and later by turning to the side. There was little or no plasticity in the extensor hypertonus in any of the animals when on their backs and it was impossible to pose any of them in the trough.

*Feeding, gastro-intestinal tract.* With the exception of one cat which ate meat on the first postoperative day and drank milk on the second, the animals would not eat meat spontaneously until the fourth to sixth postoperative day and would not drink milk until the sixth to eighth day. All would chew and swallow meat placed in their mouths two or three days before they began to eat spontaneously. In eating meat some of the animals licked the meat into their mouths, while others made lunging bites and swallowed the mouthful obtained without chewing. They would indiscriminately bite or lick the edges of the pan. All of the animals lapped milk, often lapping the edge of the pan or the air, or dipping the nose far into the milk. When feeding, the animals frequently made treading or pawing movements with the forelimbs, placed the forefeet in the dish, and sometimes purred or growled. They appeared very hungry.

The same two cats which lost their over-activity and disposition to follow quickly acquired better eating habits than their fellows. The animal which ate from the first postoperative day was not a member of this group, however.

The stomach and intestines of each animal were examined at autopsy, but the results do not compare favorably with those of Mettler, Spindler, Mettler and Combs ('36) who found gastric hyperemia and ulceration following bilateral removal of the frontal lobes in the cat. A single ulcer was found in the pyloric region of the stomach of the animal which died on the sixth postoperative day. This consisted of an area of mucosal erosion about 2 mm. in diameter with slightly elevated and pinkish margins. We question its relationship to removal of the frontal lobes, however, for the stomach and intestines of all the other animals were normal.

*Emotional behavior.* We cannot agree with Barris ('37) that there is any more than a very transient impairment in the emotional reactivity of these animals. The response to pinching the tail was uniformly weaker than normal during the first, second and third postoperative days. It regained a normal vigor during the fourth to sixth days, however, and on pinching the tail the animals cried loudly, spit, circled and in some instances attempted to strike the observer's hand.

Three of the cats exhibited an aversion to their fellows from the third postoperative day onward. One of these animals, when another cat approached her on the third postoperative day, rolled onto her side, extended the limbs in front of the fore part of the body, with the digits spread and claws bared, and repeatedly struck with the uppermost forelimb; the ears were retracted, the pupils widely dilated, the cat spit several times and for a short time afterward growled intermittently.

The animals showed every indication of marked emotion when in a room with barking dogs in cages, but unfortunately this was not tried until most of the animals were in their first or second week of survival, and the earliest test was on the sixth postoperative day. In this instance the cat faced the dog which was barking the loudest and remained in the center of the room, with

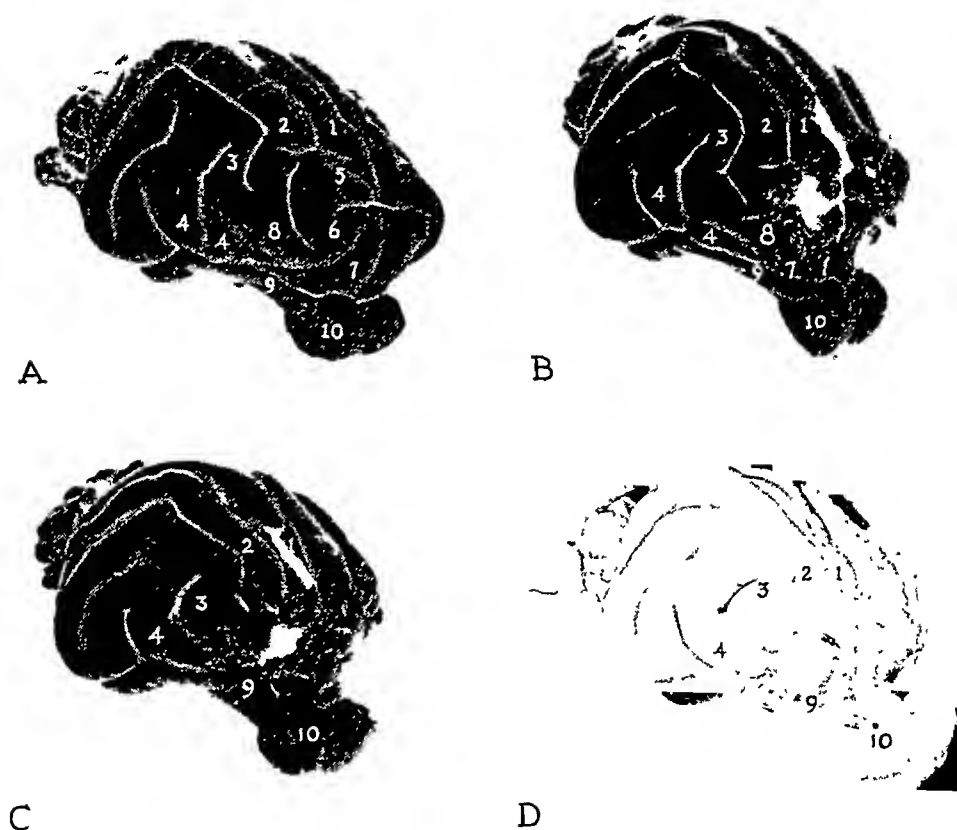


FIG. 1. Photographs of brains of: A, normal cat; B, Cat 1; C, Cat 2; D, Cat 3. The numerals have the following significance: 1, lateral gyrus; 2, middle suprasylvian gyrus; 3, anterior ectosylvian gyrus; 4, anterior sylvian gyrus; 5, posterior sigmoid gyrus; 6, anterior sigmoid gyrus; 7, frontal gyrus; 8, coronal gyrus; 9, olfactory stalk; 10, olfactory bulb.

its limbs extended, back arched, and tail vertically upright. The hair on the back and tail was maximally erected and the pupils maximally dilated. The cat's repeated, explosive spitting could be heard above the noise of the dogs. The cats with longer survival times exhibited just as normally vigorous pilomotor, pupillary and facio-vocal activity but instead of assuming the Halloween posture just described, crouched and retracted the forequarters

and head, and two of the animals subsequently turned and ran out of the room.

With the possible exception, however, of the three cases which were antagonistic toward their fellows, a trait occasionally present in the normal cat, these animals have not impressed us as possessing the intense emotional hyper-excitability seen in the completely decorticate cat (Bard, '28; Bard and Rioch, '37).

The animals showed a pronounced affection toward the observer. They circled, arched and rubbed themselves against the observer when petted, often purring and making treading movements with the forelimbs, and when studying the animals it was difficult to take notes with the cats on the table as they would not stay away from the observer.

*Extent of ablation.* In all of the animals the posterior sigmoid, anterior sigmoid and most of the coronal and frontal gyri (terminology after Papez, '29) were removed bilaterally. In the two animals which recovered from an initial over-activity and tendency to follow, and which regained essentially normal eating habits, this was the extent of the area ablated, as is seen in the photograph of the brain of Cat 1, shown in Fig. 1B. The extent of ablation can be determined by a comparison with the normal brain shown in Fig. 1A.

In the remaining four animals the ablation was slightly more extensive so that the anterior ends of the lateral, middle suprasylvian and anterior ectosylvian gyri were removed and all of the coronal gyri and the anterior half to two-thirds of the anterior sylvian gyri were bilaterally ablated. Even the most ventral portions of the frontal gyri were either removed or disconnected from more caudal regions. In three of these animals the olfactory tracts were considerably injured on one or both sides, as in Cat 3, whose brain is shown in Fig. 1D, but in one animal, Cat 2, whose brain is shown in Fig. 1C, they appeared intact and it was this cat which ate from the first postoperative day. All four of these animals, however, showed persistent impairments in feeding habits, a deficit which has been attributed by Langworthy and Kolb ('35) to removal of the electrically excitable cortical field for masticatory and lapping movements located in the region of the rostral end of the anterior sylvian gyrus (Magoun, Ranson and Fisher, '33; Ward and Clark, '35; Tower, '36). The present results, as far as they go, support this interpretation, but isolated removal of this field might be expected to yield more critical information.

### SUMMARY

A description is given of the pronounced activity, loss of postural reactions, extensor hypertonus without plasticity, impairment in feeding and retained emotional behavior of cats following bilateral one stage removal of the frontal lobes of the cerebral cortex.

This description appears essentially identical with that presented by Langworthy and Kolb ('35). The cataleptic phenomena described by Barris ('37) were not observed.



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# FORCED CIRCLING IN MONKEYS FOLLOWING LESIONS OF THE FRONTAL LOBES\*

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PRIMATES from which the cortex of one cerebral hemisphere has been removed circle in walking toward the side of the lesion; such animals also show contralateral hemiparesis together with deviation of head and eyes toward the side of the lesion. With all types of progression there is rotatory movement which appears to be involuntary and purposeless and becomes accentuated under emotional stimuli such as rage, fear, or the sight of food. Deviation of head and eyes, and circling occur in hemidecorticate cats and dogs, as well as in subhuman primates. After lesions of the frontal lobes, Hitzig (16) observed the same symptoms in dogs and attributed the phenomena to paralysis of the trunk muscles of one side. In 1895 Bianchi (3) noted that monkeys with "pre-frontal" ablations circle toward the side of the lesion, due, he thought, to visual and to "intellectual" disturbances. In man also conjugate deviation of the head and eyes appears after certain cortical lesions, and many focal epileptic attacks begin with turning of head and eyes (10).

In the following experiments an attempt has been made to analyze in the monkey (*Macaca mulatta*) the physiological factors involved in circling, and to localize the cortical area responsible for this symptom.

## METHODS

In the present study lesions of area 8 were made in 12 normal rhesus monkeys (*Macaca mulatta*). In addition observations were made on a large number of monkeys, with lesions elsewhere in the cortex which had been operated on for other purposes. Excisions of cortical areas were made under aseptic technique and the animals were observed subsequently over a period of several months.

## PRELIMINARY CORTICAL ABLATIONS

In attempting to determine the region of the brain responsible for circling and head turning observations were made on animals with lesions involving various cortical areas. As these studies have an important bearing upon area 8 ablations to be described below, they may be briefly summarized.

*Hemidecortication.* The symptoms following hemidecortication in the monkey are well known (Hitzig, 16, Karplus and Kreidl, 19). A profound contralateral hemiparesis develops immediately together with a sensory deficit and hemianopia. The phases of recovery are also predictable, during the *first week* power returns to such an extent that the animal is usually able to sit and stand, and even to walk and climb awkwardly. The paretic extremities, at first flaccid, begin to show spasticity at about the third day and tend then to be held in greater extension than the normal limbs. They are less sensitive to touch and to pain on the affected side than on the normal, and the sensory deficit is also evident in progression for the animals tend to "lose" the extremities, which become tangled in awk-

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ward postures. Forced grasping is prominent and tendon reflexes, at first decreased, tend ultimately to become exaggerated on the paretic side. Deviation of the head and eyes and curving of the body are marked as soon as the animals regain their feet; any emotion, excitement, fear, or rage accentuates the head deviation and tendency to circle. Although the head and eyes are usually held toward the side of the lesion, they are frequently turned in the opposite direction when the animal is not under stress, and immediately after operation the eyes can be fully deviated in both directions.

By the end of the *first month* improvement is considerable, but movement and posture in the paretic limbs are not normal, for there is persistent spasticity with hyperactive tendon reflexes; the sensory deficit to touch and pain is less marked. No fine movements are performed with the paretic hand or foot, and fingers and toes can not be used individually. All purposeful movements are executed either by the normal side alone, or by the normal extremities first, followed and assisted by the paretic members. At this stage deviation of the head and eyes is less marked than after operation, but is still conspicuous. The animal tends to look toward the normal side and to circle in this direction, but at times is able to move forward in a straight line.

Recovery in both motor and sensory spheres continues slowly but steadily after this for at least the first six months. Motor deficit, hemianopia and a tendency to circle have been observed to be present for a year; indeed the symptoms probably persist indefinitely, for the hemidecorticate macaque reaches a permanent motor status which can never be mistaken for normal.

In such animals the circling has been attributed to visual abnormality (Karplus and Kreidl, 19). Hemianopia, together with deviation of the eyes to the "seeing" side might produce a turning of the animal toward the objects seen. However several of these animals in which circling movements were present were blindfolded without altering motor performance. On one, a hemidecortication was performed some time after the opposite occipital lobe had been ablated. This blind animal also circled.

*Frontal lobe.* Isolated extirpation of the frontal lobe in monkeys (areas 4, 6, 8, 9, 10, 11 and 12) produces similar forced turning with deviation of head and eyes. These symptoms however are neither as extreme nor as enduring as in the hemidecorticate preparations and recovery from the hemiparesis also is quicker and more complete. During the first postoperative week the monkey without one frontal lobe recovers sufficiently to walk, climb and run adequately, although all movements on the paretic side show clumsiness and incoördination, spasticity and hyperextension. The fingers and toes are not used for fine movements at this stage. Forced circling is conspicuous as is deviation of the head and eyes; these last symptoms are present for several weeks but become less noticeable during this interval. A tendency to rotate when excited persists for months, being detectable long after deviation of the eyes or head has entirely disappeared.

The "visual" defect present following frontal lobe ablation will be described later in the discussion of the effects of lesions of area 8.

*Areas 4 and 6.* Ablation of the motor and premotor areas (areas 4 and 6, upper part, Fig. 1) together or in series, is followed, as is well known, by contralateral motor paresis (11). It has been suggested that circling movements occur because of weakness of the extremities of one side; however, these animals show no circling even at the height of their motor paresis. After isolated ablation of face and neck fields (areas 4 and 6, lower part), the resultant imbalance of the neck musculature does not cause forced circling and the head and eyes remain in the mid-line in spite of noticeable facial weakness.

*Ablation of the remaining parts of the frontal lobe exclusive of areas 4 and 6* (i.e., areas 8, 9, 10, 11 and 12), is always accompanied by deviation of the head and eyes, and by forced circling *without attendant paresis of the face and limbs*. When various of the frontal association areas were then ablated singly and seriatim it developed that removal of fields 9, 10, 11 and 12 caused no one of the three symptoms, and that motor performance following such ablation could not be differentiated from that of a normal animal.

*Other cortical areas* Removal of an occipital lobe is followed by hemianopia which differs from the visual defect of frontal lesions in that it is a permanent object-vision blindness. Such hemianopia is not accompanied by forced turning. There are times when these animals turn, because, as is obvious in watching them, they can see only to one side, and must therefore look only in that direction. The performance, however, is quite different from the regular circling movements of which follow ablation of a frontal lobe with area 8 removed. In true hemianopia turning is only occasional and is clearly visual in origin, it is never purposeless.

The effect of removal of the other centers for eye movements (Graham Brown, 12) has not as yet been investigated fully. In a few animals from which the parietal lobe had been removed and in which there was no hemianopia, deviation of the head and eyes has been noted, but without the forced and purposeless turning movements.

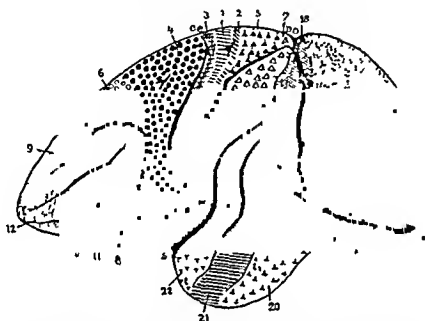


FIG 1 Brodmann's cytoarchitectural map of monkey's brain (cercopitheque). Extirpation of the region indicated here as area 8 leads to forced circling syndrome in the macaque.

### ABLATION OF AREA 8

Ablation of a small area inside the curvature of the arcuate sulcus of the macaque (Fig. 2) roughly corresponding to area 8 of Brodmann (Fig. 1) is invariably followed by a definite syndrome which includes turning of head and eyes and circling. Area 8 as described by Brodmann in cercopitheque lies within the arcuate sulcus along its anterior lip (Fig. 1). Stimulation of this region produces movement of the eyes—usually conjugate—horizontal and away from the side stimulated, and is followed after an interval by turning of the head as well. Mesial to the arcuate sulcus in an area corresponding with the junction of areas 6 and 9, eye and head movements can also be obtained by stimulation. Here the head movement is most often primary and followed by that of the eyes. Widening of the pupils is also produced on stimulation here (Graham Brown, 12; Beevor and Horsley, 2; Leyton and Sherrington, 21; Wilbur Smith, 26). The mesial limb of the arcuate sulcus in the macaque is very deep and extends both mesially under area 6 and caudally deep to area 4. It is variable as to exact shape and depth as are all the cortical sulci in this species. Lesions of area 6 on the mesial side of the sulcus produce no turning

of the head and no eye symptoms, unless area 8 as well is inadvertently damaged.

*Unilateral ablation.* Unilateral excision of the region anterior and lateral to the arcuate sulcus (i.e., area 8) is followed by deviation of the head and eyes and circling progression toward the side of the lesion. The symptoms are

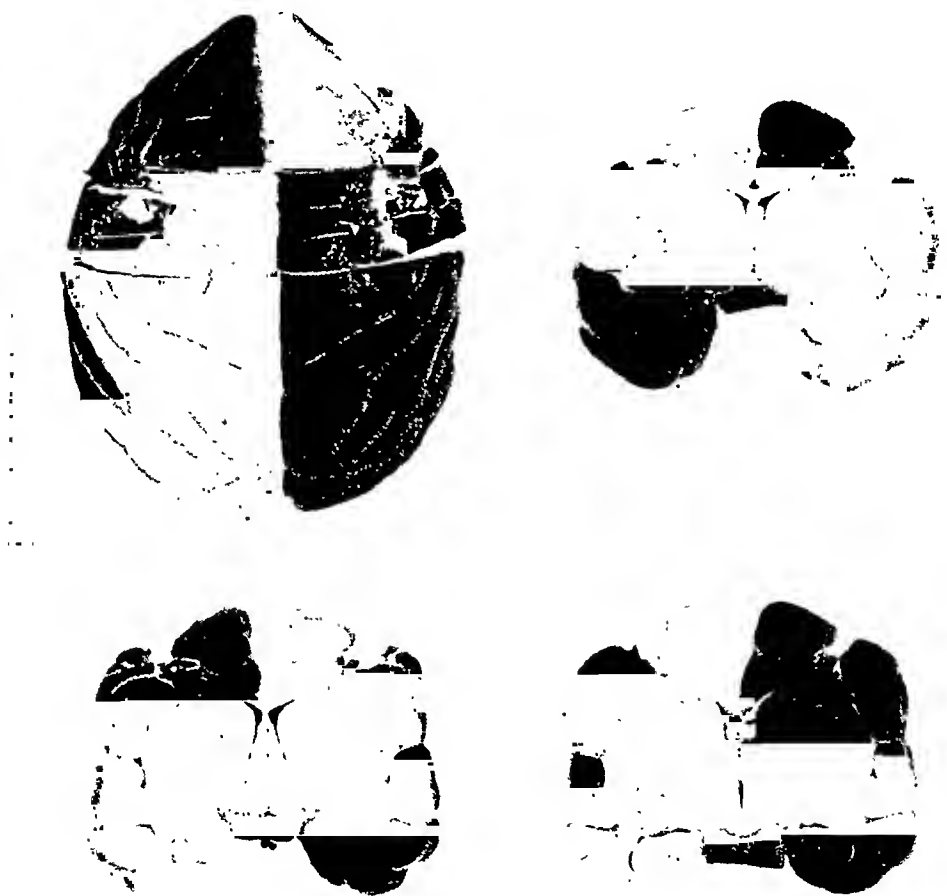


FIG. 2. Brain of a macaque (*M. mulatta*) after bilateral extirpation of area 8 showing extent of lesion into depths of sulcus, but without injury to caudate sulcus.

extreme during the first two or three postoperative days and all motor progression is accompanied by circling and turning of the body. During the succeeding two or three weeks the eye and head turning gradually becomes less and then disappears. A tendency to circle toward the side of the lesion persists for several months. However, this syndrome occurs only if area 8 is removed in its entirety, including all the gray matter in the depths of the arcuate

ate sulcus. Removal of the superficial cortical tissue produces only a fleeting trace of the syndrome.

The term "forced circling" has been used to describe this performance both because the animals are unable to move except in circles, and also because they seem to move more but with less purpose than the normal animals; thus, any emotional stimulus incites great motor activity and consequent revolving of the animal. When the conjugate deviation and the circling have disappeared the purposeless activity continues and the animals are restless, easily excited and hyperactive. At no time do they show any abnormal posture or paresis of the extremities.

In addition to the above symptoms these macaques present a transient condition which is difficult to distinguish from hemianopia. That is, they apparently do not see in the contralateral visual fields. They pay no attention to food placed in this side of their cage, they do not respond by blinking to threats made in this field and when small bits of food are brought into the field of vision from this side no response occurs until the mid-line of vision is approached. This defect disappears gradually, but persists for a time after the disappearance of conjugate deviation. The duration and intensity of the abnormality are both affected by lesions elsewhere in the frontal lobe, for the deficit lasts longer and is more pronounced following frontal lobe extirpation than after ablation of area 8 alone.

*Bilateral ablation.* If area 8 is removed first from one side and then from the other the same syndrome develops; after the symptoms from the first ablation become less marked, removal of the second area will temporarily reverse the direction of head and eye deviation, and of circling movements.

When area 8 is ablated from *both sides simultaneously*, or one shortly after the other, the picture which develops is striking, and quite different from that seen following any other type of discrete cortical extirpation. Immediately following operation such animals show all the motor symptoms seen after bilateral extirpation of the frontal association areas plus area 8. There is no paresis or postural deficit but the animal sits motionless at first. The head is sunk between the shoulders, and the gaze fixed and straight ahead; blinking is infrequent, movements of the eyes are almost absent. Eye movements in either direction are possible, for the eyes tend to follow an object, but always return to a fixed central stare. Such animals sometimes appear to be blind, although they follow moving objects and although visual stimuli produce frequent rage reactions. They walk into objects, forcefully striking their heads against the side of the cage. They will reach for and grasp any type of object offered, but then do nothing with it. It is difficult to feed them for they do not seem to know what to do with food. This inability to appreciate objects in the normal manner seems to be due to tactile as well as to visual disturbances for many times things held in the hand are not recognized.

During the first week these animals become more alert and begin to distinguish between objects seen. After a period of a few weeks they become nearly normal except that they continue to have a "wooden" expression and

fixed gaze. Circling movements in bilateral preparations occur and may take place in either direction, the animals often turn one way and then reverse and turn the other for a time. The circling is not as prominent as it is in the unilateral preparations, but the stereotypy and the forced character of all movements are conspicuous and there develops a restless and purposeless behavior in which the general activity seems to be increased.

### DISCUSSION

Discrete ablation of area 8 in the monkey is thus followed by a definite syndrome which is composed of two groups of symptoms: first a change in motor activity which consists of involuntary circling, appearing in the absence of postural or paretic changes in the extremities; and second, a defect in the visual apparatus consisting, when the lesion is unilateral, in: (a) a deviation of the eyes toward the lesion, and (b) a contralateral defect in vision. The two groups of symptoms are always part of the same syndrome for neither occurs in animals in which the other has not also existed. The symptom complex seems to be identical with that described by previous authors in animals from which all tissue rostral to the motor areas has been removed (Bianchi, 4), although in the present series only the small portion of these areas known as area 8 is injured.

Histological identification of this cortical area is at present difficult. Grossly it is well defined in the macaque (Fig. 2) as the region lying within the arcuate sulcus—that is, anterior and lateral to the sulcus, and roughly corresponding to the area 8 demarcated by Brodmann for the cercopitheque. The histological structure of this area is transitional from the agranular motor cortex of area 6 to the granular cortex of the true frontal association area 9 (von Economo, 27; Campbell, 6).

The cytoarchitectural maps of both Mauss (22) and Brodmann (5) have confined the limits of area 8 within the arcuate sulcus in the monkey. In the higher apes and in man, however, this area extends to the mid-line, rostral to area 6 (Brodmann, 5; von Economo, 27; Foerster, 10), and Hines has stated that in the macaque as well a strip of tissue which is cytoarchitecturally indistinguishable from area 8 of Brodmann runs mesially from the arcuate sulcus to the mid-line (13).

The physiological evidence is also that this region extends to the mid-line in macaque, anthropoid, and man, for eye movements may be elicited from stimulation of all of this strip of tissue although their character changes in the different parts, much as in areas 6 and 4 specific regions subserve different muscle groups for limbs. On the other hand removal of the mesial part of this strip designated to area 6 is followed by no appreciable alteration in head or eye performance. The forced circling appears only when the more lateral part now designated as 8 has been damaged.

*Motor defect.* In 1868 J.-L. Prévost published a Paris thesis entitled: "De la déviation conjuguée des yeux et de la tête dans certains cas d'hémiplégie" (24). In it he cites 58 human cases of hemiplegia, which showed deviation of

the head and eyes. The lesions were widely distributed within the central nervous system and were for the most part diffuse—four only being limited to cerebral cortex, and only one to the frontal lobe. He also cites the scanty experimental literature concerning deviation of the head and eyes in animals; symptoms infrequently noted at that time following cerebral hemispherectomy and remarks on the circling movements which accompany this deviation.

In 1874 Hitzig (15), and in 1875 Ferrier (7) first elicited movements of the eyes from stimulation of the cerebral cortex. The region of the sigmoid gyrus of the dog (Hitzig) and the "base of the superior frontal convolution" in the monkey (Ferrier, 8) were the regions from which such movements were produced. In human beings deviation of the head and eyes have long been known to accompany hemiparesis, and to be a part of some attacks of Jacksonian epilepsy. In 1926 Foerster (9) was able to stimulate a series of human brains under local anesthesia, and then reported conjugate turning of the eyes from stimulation of areas 8a, 8 $\alpha$  and 8 $\beta$ , and, from the region more mesial (area 6a $\beta$ ), adversive turning of head, eyes and body.

In the lower primates, the monkey or anthropoid, functional differentiation here, as in other regions of the cortex, is not so discrete as it is in man. After stimulation of more lateral cortical eye centers of the monkey (area 8) eye movement is primary, and followed often by head. Repeated stimulation of the anterior portion of area 6, on the other hand, will in the same animal, tend to give primary head movement, which is followed by movement of the eyes. It is rare, however, in these animals that movement of the head can be produced without eye movement as well.

*Activity.* Greater specificity of cortical localization in the human is further demonstrated by the fact that increase in motor activity has never been correlated with head and eye deviation in man whereas in the monkey after lesions of area 8 one is accompanied by the other. In man, hyperactivity is known to be a factor in certain types of "mental" disorders such as the overactivity of the manic, or the restlessness of some post-encephalitic patients, and these changes have been attributed to changes in the frontal lobe, but no more discrete localization has been possible.

In animals, restlessness and an increase of purposeless activity following bilateral frontal lesions are described by many authors (Hitzig, 16; Bianchi, 4). Jacobsen (17) has found it in lesions limited to the frontal association areas in monkeys; and recently Richter and Hines (25) have observed hyperactivity following both prefrontal and striatal lesions in monkeys. They find that in pure cortical lesions removal of area 9 alone produces maximum hyperactivity, although some appears following lesion of area 8 as well, but that the greatest increase is seen only when the tip of the caudate nucleus is damaged. They do not record associated turning movements. At present, in our studies, there is evidence to indicate in corroboration of Richter and Hines, that there is greater increase in activity following extirpation of all the frontal association areas together with area 8, than of area 8 alone, and that this may occur



without injury to the caudate. Further investigation of this point is in progress. The head and eye symptoms which follow discrete lesions of area 8 are also pronounced and more enduring when other parts of the frontal lobe are removed in addition to area 8 (18). The motor eye fields of parietal and occipital lobe (Graham Brown, 12), probably also play a part in the intensity of this reaction.

*"Visual" defect.* The nature of the disturbance in response to visual stimuli as a component of this syndrome is difficult to explain. The head and eye deviation may be produced by removal of normal motor innervation to the muscles of the head and eyes and may thus be analogous to the paresis induced by removal of a specific part of the true motor areas 4 and 6. In this respect area 8 is a region elaborating complex motor performance for the head as does area 6 for the extremities. The unilateral visual defect is more difficult to analyse. It is of such a nature that objects in the contralateral field of vision are disregarded. Since, however, the defect is transient, and, when bilaterally present, does not result in blindness, it cannot be a defect in the afferent visual apparatus as in true hemianopia due to occipital lesions. Similarly, it cannot be merely an *apparent* visual defect due to loss of motor power in eye muscles, since eye movements are present in all directions at a time when the visual defect also exists. Unilateral absence of the blink response to threat at a time when other types of lid closure are bilaterally equal also precludes pure motor deficit. The defect obviously lies in the cortical connections between sensory and motor regions, and it can only be described at present as a lack of recognition of or an inability to respond to afferent visual stimuli.

There are a number of earlier descriptions of "hemianopia" related to lesions of the frontal lobe. In 1895 Bianchi, extirpating one frontal area in monkeys, described a visual defect which he recognized as transient, and which he thought to be a hemianopia. The dogs of Minkowski (23) and of Hitzig (16) exhibited unilateral visual defects after lesions in one sigmoid gyrus. L. Bard (1) in 1904 described such an abnormality occurring in association with conjugate turning of the eyes and head in hemiplegic humans. These patients, like our monkeys, did not blink in response to threat in the defective eye field. Bard believed that the defect was sensory.

*The bilateral syndrome.* The striking alterations in general performance of animals after bilateral removal of area 8 is in every respect like that following ablation of all the frontal lobe areas exclusive of 4 and 6. Bianchi marvels at his monkeys in this state, and at the great "intellectual" deficit which they display as they sit motionless and apparently dazed following operation, and then evolve a purposeless overactivity and tendency to rage. The same emotional instability has appeared to a marked degree in our animals.

We have as yet no evidence as to the relationship of changes in activity to caudate injury such as have been described by Richter and Hines (25), for, in the present series, the caudate nucleus was not damaged. In view of the physiological and direct anatomical connections which exist between area 8 and the striate nuclei (Hirasawa and Kato, 14), it is pertinent to draw at-

tention to the similarity in symptoms between the monkey deprived of area 8 and the human post-encephalitic in whom striatal disease is present. Restlessness, "driveness," immobility of facial expression and noticeable diminution of blinking and of eye movements are symptoms which may be common to both conditions.

It is of interest also that much of the "stuporous" behavior described in frontal animals is undoubtedly due to disorder of the components discussed in this paper. Clearly the bilateral production of this visual deficit might result in the tendency to sit still, to walk slowly, to bump into objects and to blink seldom in response to threat. Thus also the circling of the unilaterally ablated preparation which appears in relation to deviation of the eyes and head, and which is of a forced and purposeless nature may, in the bilateral preparation, result in the constantly increasing forced overactivity of the first postoperative months.

### SUMMARY

1. The unilateral and bilateral ablation of area 8 in monkeys is followed by a characteristic syndrome similar to that produced by removal of the entire frontal lobe, rostral to area 6 (areas 8, 9, 10, 11 and 12).

2. A deviation of the head and eyes toward the side of the lesion is produced by lesions of area 8, which becomes less marked during the first post-operative weeks. A tendency to turn the head in this direction persists much longer.

3. Forced purposeless circling movements appear coincident with head and eye deviation. They also diminish in intensity but persist as hyperactivity for as long as a year.

4. A "visual" defect is present contralateral to the lesion which is not a hemianopia but which has to do with inability to respond to visual stimuli.

5. The picture of "intellectual" deficit described by Bianchi following bilateral frontal lobectomy may be attributed to the alterations in vision and in motor performance just described.

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# THE REPRESENTATION OF RESPIRATORY MOVEMENTS IN THE CEREBRAL CORTEX

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## I. INTRODUCTION

MOST previous studies on the control of respiration by the central nervous system have centered mainly around the myelencephalic "respiratory center." In contrast to the exact knowledge which we possess concerning the manner in which breathing is regulated by the "respiratory center," little is known concerning the rôle of the higher parts of the brain in the phenomenon of respiration. The fact that man can voluntarily alter the rate and duration of either one or both of the respiratory phases, that he can change the respiratory rhythm and can even voluntarily arrest respiration for a certain length of time indicates that the cerebral cortex exerts an influence on respiratory movements. In addition, it is an observable fact that mammals in general, in the waking state, modify their respirations in various ways and it seems possible that these modifications are influenced by impulses from the cerebral cortex. If one assumes that the cortex is not equipotential in its ability to alter breathing, then certain areas ought to be found that are able to produce reasonably constant alterations of the respiratory movements when electrically stimulated under uniform experimental conditions, but the reports of previous investigators have been so at variance with one another that one is unable to determine from them precisely what areas of the cortex are concerned.

## HISTORICAL NOTE

Lepine, in a communication to the Société de Biologie in 1875, is reported to have stated that excitation of the anterior part of the cerebral hemispheres in the dog slows and even arrests respiration. Since this report investigators have published data which indicate that alterations in breathing can be obtained from widely separated parts of the cortex. Bochefontaine (1876) obtained irregular and inconstant alterations from stimulation of "those points that have an action on movements of different parts of the body." François-Franck (1887) contended that respiratory alterations could be obtained only from the sigmoid gyrus in the dog and cat and that no correlation existed between the point stimulated and the resultant response, weak stimuli were found to produce acceleration, strong stimuli a slowing. Danilewsky (1875) in three instances obtained slowing or arrest of breathing in the cat and dog from stimulation of an area in the suprasylvian gyrus. Unverricht (1888, 1897) using dogs was unable to confirm the findings of Danilewsky, but he located an area in the ectosylvian gyrus from which slowing or arrest of respiration was obtained. Preobraschenski (1890) confirmed Unverricht's findings in the dog, and in the cat he located two cortical respiratory areas, one near the rostral end of the suprasylvian sulcus produced arrest of the thorax in expiration, the other a short distance caudad produced arrest in inspiration. Bechterew (1911) from his work and that of his associates confirmed Preobraschenski's findings in regard to the area for expiratory arrest in the cat. In the dog he found two areas which responded with slowing or arrest of respiration, one in the rostral part of the suprasylvian gyrus from which arrest in expiration was obtained, and another near the end of the sulcus praesylvius which caused slowing or arrest in inspiration. Stimulation of an area in the most lateral part of the anterior sigmoid gyrus caused an increase in frequency of the respiratory movements. Munk (1882)

and Gianelli (1900) in the dog located areas in different parts of the cortex which produced an inhibitory response like that described by Bechterew and which they believed controlled the activity of either the inspiratory or the expiratory muscles.

Spencer (1894) in the cat and dog obtained slowing or arrest of respiration from an area including the caudal and lateral part of the olfactory tract and a small area of the laterally adjacent cortex. Increase in the rate of breathing was obtained in lightly anesthetized cats and dogs over a wide extent of the cerebral surface, but under deeper anesthesia this effect was most marked when the stimulus was applied to the cortex around the medial end of the sulcus praesylvius. Mavrakis and Dontas (1905) confirmed this latter finding on the dog. Bucy and Case (1936), in the dog, obtained slowing or arrest from an area adjacent and lateral to the rostral end of the coronal sulcus and an increase in rate from the lateral part of the anterior sigmoid gyrus.

Alterations in respiration from stimulation of the cerebral cortex in monkeys have been reported by Munk (1882), Spencer (1894), Bechterew (1911) and C. and O. Vogt (1919). Munk (1882) obtained arrest of respiration with the respiratory muscles in tetanic contraction from stimulation of the cortex just rostral to the curve of the inferior precentral sulcus and just medial to its medial end. Spencer (1894) reported arrest or slowing from stimulation of a large part of the orbital surface of the frontal lobe, the area from which the response was most easily obtained being just anterior to the junction of the lateral olfactory striae with the gyrus hippocampus. Bechterew (1911) obtained arrest of respiration in inspiration upon stimulation of an area a little anterior to the medial end of the sulcus precentralis inferior and an increase in rate from the cortex a little lateral to this area. C. and O. Vogt (1919) observed arrest or slowing from stimulation of the cortex just behind the lateral end of the sulcus precentralis inferior.

An analysis of the results of these investigators shows that they are far removed from unanimity not only as regards the position and extent of the cortical respiratory areas but also as regards the character of the elicitable response. In my investigations on the cat, dog, and monkey (*Macaca mulatta*) definite regions of the cortex were found which, when electrically stimulated, evoked specific alterations of the respiratory movements. Certain regions were found to have a predominantly inhibitory effect; others a predominantly excitatory effect. The inhibitory response was characterized usually by a slowing or complete arrest of breathing, and occasionally by a marked decrease in the amplitude of the respiratory excursions. The excitatory effect, on the other hand, was characterized by a marked increase in the rate of breathing. Although the responses obtained at different times varied in details, they did not depart from these fundamental characteristics.

## II. EXPERIMENTAL PROCEDURE

The usual technique for cortical stimulation was employed, the animal being kept under light ether anesthesia and stimulation of the cortex performed with 60 cycle alternating current using bipolar platinum electrodes 0.7 mm. in diameter and approximately 2 mm. apart. The electrodes were usually applied by hand, but in some instances they were carried by means of a suitable holder attached to a modified Horsley-Clarke stereotaxic instrument. The application of the electrodes by this method was found to possess certain obvious advantages not attainable by hand exploration, since they can be applied without undue pressure on the cortex, and being attached to the head of the animal, move with the head, thus avoiding risk of injury to the cortical surface. The anesthetic was administered from a Woulff bottle connected to a

rubber tube introduced through the mouth and larynx into the trachea. An uninterrupted passageway for air was thereby ensured and alterations of breathing from closure of the larynx were thus obviated.

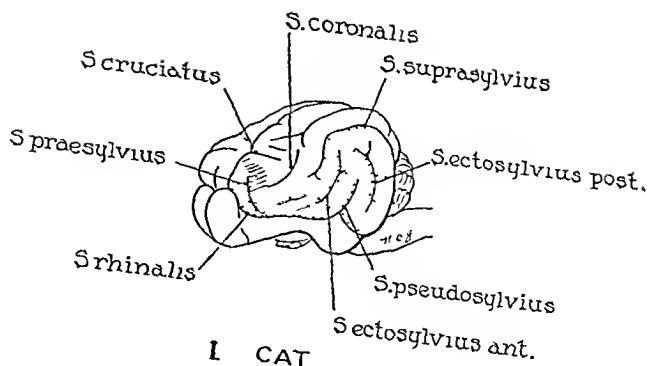
A closed system for recording the respiratory movements was used, because an open method like the one commonly employed was not found to give an accurate record, since its action depends upon intratracheal pressure changes rather than increase or decrease in the size of the thorax during the respiratory act. Accordingly, for the purpose of obtaining a kymographic record the tambour was connected to two rubber sphygmomanometer bags held in contact with the thorax and abdomen by an inelastic canvas belt, and inflated to the necessary degree. By this method inspiration compresses the bags and produces the upstroke on the record, expiration permits the compressed bags to relax and produces the downstroke. If desired, abdominal and thoracic respiration can be recorded separately. The whole system is sufficiently free of inertia to follow rapidly whatever changes in breathing occur. The arterial pressure was recorded from the femoral artery simultaneously with the respiration. The time in seconds and the duration of the stimulation were recorded by appropriate methods.

The extent of the responsive cortex was plotted on a tracing or drawing of the cortical surface and at the conclusion of the experiment the brain was fixed in 20 per cent formalin, after which blocks were taken, embedded in paraffin, serially sectioned at 20 microns and stained with thionin for cyto-architectural study.

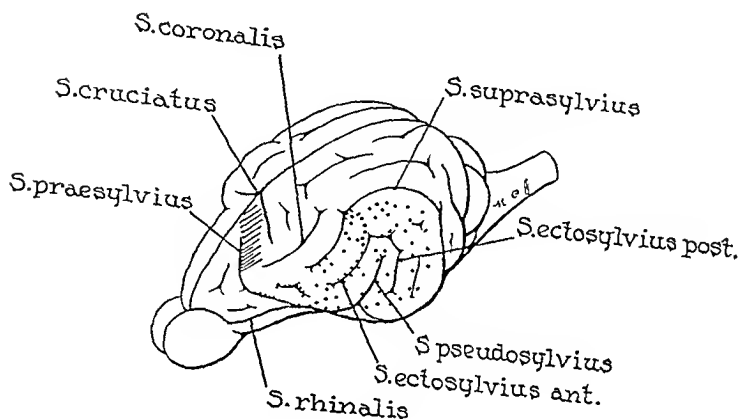
### III. RESULTS

#### *Inhibition*

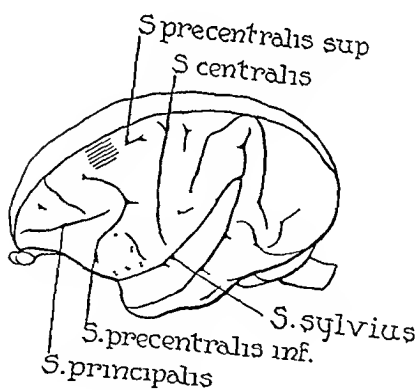
In the cat and dog (Plate 1, Figs. 1 and 2) an inhibitory response was obtained from a relatively large area of the cerebral cortex when the animal was under very light ether anesthesia, the position of the inhibitory cortex being similar in the two species except as regards the cortex of the gyrus proreus. In the cat this gyrus usually gave an inhibitory response, but in the dog no respiratory effect was produced by its excitation. Increase in the depth of anesthesia resulted in decrease in size of the excitable field and finally in abolition of the response, an area in the anterior composite gyrus just caudal to the sulcus praesylvius being the last to succumb. This area is also the one from which an inhibitory response was most easily elicited, it having the lowest threshold of excitability, and it was from this area that arrest of breathing was most easily obtained. A stimulus of just sufficient strength to produce arrest here caused only a decrease in rate when applied to the more caudally situated part of the inhibitory field, and in general the effect became progressively less marked as the caudal edge of the field was approached. The one exception to this is furnished by a small area in the caudal part of the anterior ectosylvian gyrus (Plate 1, Figs. 1 and 2) for this area appears to have a lower threshold than the adjacent inhibitory field and produces a greater inhibitory effect when stimulated. However, it was never found to be such a powerful inhibitor as the area in the anterior composite gyrus.



1 CAT



2 DOG



3 MONKEY

- - Inhibitory cortex  
 ■■■■ - Acceleratory cortex

PLATE I

Areas of the cerebral cortex from which alterations of respiratory movements were elicited by electrical stimulation. The closest stippling and the closest lines indicate the areas from which the responses were most easily obtained.

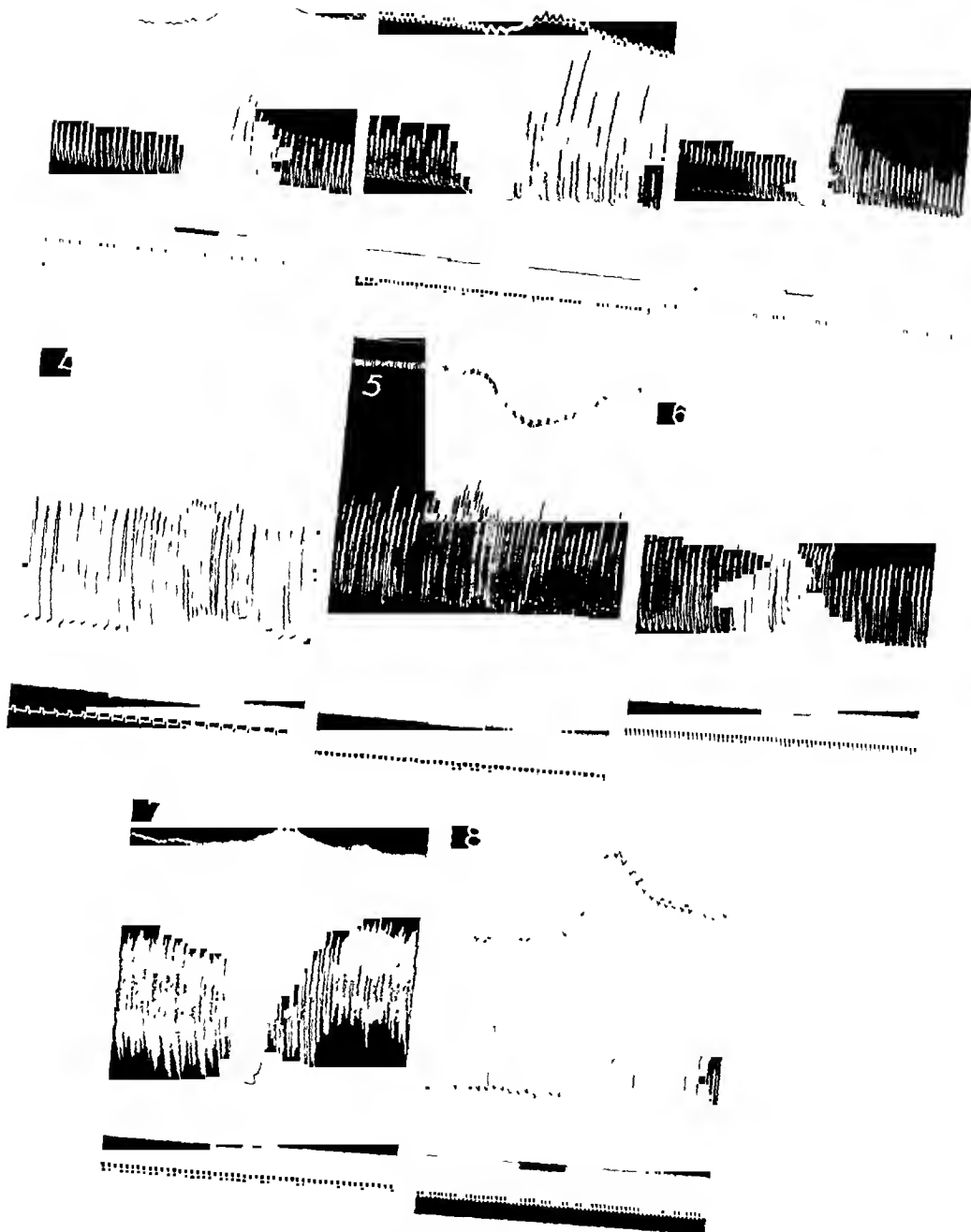
Stimulation of the inhibitory area in the anterior composite gyrus of both cat and dog with current of a strength from 0.2 to 2 milliamperes, depending upon the degree of anesthesia, evoked an apparently immediate inhibitory response characterized by the thorax assuming the expiratory positions and maintaining this throughout the period of stimulation, provided the duration of the stimulation was not too prolonged (Plate II, Figs. 1 and 2). Upon cessation of the stimulus breathing was again resumed, often for a few seconds at a higher inspiratory and expiratory level than that which existed previously or there was an immediate return to normal without such a transition. This complete cessation of respiration could not be prolonged indefinitely, for after several seconds breathing begins again, although at a much slower rate than that existing prior to the application of the stimulus. An inspiration of great depth frequently initiated respiratory movements after the arrest. Deviations from this response were found to occur; for example, upon application of the stimulus the thorax sometimes assumed the expiratory position and then immediately, or after the lapse of one or several seconds of complete cessation, a slow inspiration took place over a period of several seconds, reaching a degree equal to or greater than that existing previously, after which breathing again began but at a much slower rate than before. Upon cessation of the stimulus breathing returned to the previous rate and amplitude. If a weaker current was used, or if the excitability of the cortex decreased, then a slowing of respiration occurred either with or without a change in amplitude and the response became less marked as the duration of the stimulation increased.

Application of the stimulating current at various portions of the inspiratory phase usually resulted in the termination of the process of inspiration, the thorax quickly assuming the expiratory position, after which any of the responses previously described might occur. At times, however, breathing was arrested and the thorax remained in the position it occupied when the stimulus was applied, and after cessation of the stimulus the phase which had been interrupted was completed. On the other hand, breathing may be arrested for a varying length of time, after which a slow inspiration lasting over several seconds may occur until the thorax is expanded to the same or to a greater extent than it was prior to the stimulation. If the stimulation is continued respirations are resumed at a much slower rate than that existing before the stimulus was applied or if the current is discontinued breathing rapidly returns to normal.

A less pronounced inhibitory effect was obtained from most of the cortex of the sylvian and ectosylvian gyri. Stimulation of this region with a current of moderate strength usually resulted in a slowing of respiration without much change in amplitude.

Stimulation of the cortex of the gyrus proreus on both the lateral and mesial surfaces of the hemisphere in the cat usually resulted in a pronounced decrease in the respiratory rate. Arrest of respiration was rarely obtained and the inhibitory response was elicitable only when the anesthesia was extremely light. Strangely enough no effect upon respiration was ever obtained from





## PLATE 2

Figs. 1, 2, and 3. Inhibition of respiration from electrical stimulation of the inhibitory cortex of the cat, dog, and monkey, respectively.

Figs. 4, 5, and 6. Acceleration of respiration from electrical stimulation of the acceleratory cortex of the cat, dog, and monkey, respectively.

Fig. 7. Arrest of panting from stimulation of the inhibitory area in the dog.

Fig. 8. The rise of arterial pressure elicited by stimulation of the inhibitory area in the anterior composite gyrus in a curarized cat under artificial respiration.

stimulation of this gyrus in the dog, even though stimuli of inordinate intensity were used.

The inhibitory area in the monkey (Plate 1, Fig. 3) is much more limited in extent than in either the dog or the cat and its boundary is more sharply defined. It is situated caudal to the lateral end of the inferior precentral sulcus and is limited laterally by the sylvian sulcus. Its caudal limit is frequently defined by a shallow sulcus occurring in the precentral gyrus at this point, but occasionally a decreased rate or a decreased amplitude was obtained upon stimulation just behind this sulcus. Stimulation of this area produced an inhibitory effect upon breathing similar to that obtained in the cat and the dog, i.e., arrest of breathing in which the thorax quickly assumed the expiratory position (Plate 2, Fig. 3). Resumption of breathing, subsequent to the arrest, is more frequently initiated by an extraordinarily deep inspiration in the monkey than in the cat or dog. Furthermore, if a weaker current was used or if the excitability of the cortex became lowered, stimulation usually produced a great decrease in amplitude without much change in rate, while in the cat and the dog slowing without much change in amplitude usually occurred.

The cortical respiratory inhibitory areas when stimulated not only exert their influence upon breathing of the usual type, but also have a pronounced inhibitory effect upon panting in both the cat and dog. The area in the anterior composite gyrus that is the most powerful inhibitor of normal breathing still retains its supremacy in the panting animal as evidenced by the fact that stimulation of this area with a current of moderate strength causes a cessation of panting (Plate 2, Fig. 7). In this instance as in the case of arrest of normal breathing, the thorax usually assumes the expiratory position. Stimulation with a weaker current slows but does not arrest panting and this is the result usually obtained from excitation of the remainder of the inhibitory field, only a slight effect being produced from stimulation of its caudal part.

The increase in rate and amplitude of breathing that is seen upon stimulation of a sensory nerve, e.g., the sciatic, can be abolished or diminished by stimulation of the inhibitory area, the inhibitory effect being most pronounced when the area in the anterior composite gyrus is stimulated and when the sciatic stimulus is at or just above threshold. At this level the respiratory effect of sensory stimulation is completely abolished. If a stronger stimulus is applied to the nerve the effect is diminished by cortical stimulation, and in general the stronger the sensory stimulus the less the cortical response.

#### *Acceleration*

The cortical region from which acceleration in the rate of breathing was obtained is situated in both the cat and dog in the anterior sigmoid gyrus and the immediately adjacent cortex of the medial surface of the hemisphere, the response being most easily elicited from the rostrolateral part of the gyrus (Plate 1, Figs. 1 and 2). In the cat under very light anesthesia an acceleratory effect, characterized by a very active expiration, was also obtained from a small area situated just at the rostral end of the sulcus ectosylvius anterior

between the sulcus diagonalis above and the sulcus rhinalis below. A remarkable characteristic of this area is that a complete reversal of response was obtained when the animal was under deeper anesthesia, stimulation then producing an inhibitory effect.

In comparison to the extent of the inhibitory area the acceleratory area in both cat and dog is relatively small, but it is not so disproportionately small as appears in the drawing for it extends into the depths of the sulcus prae-sylvius forming its caudal wall.

The acceleratory response in the monkey was most easily elicited from the cortex just rostral to the superior precentral sulcus and from a small area of the immediately adjacent cortex of the medial surface of the hemisphere (Plate 1, Fig. 3).

In the cat, dog, and monkey the acceleratory areas usually respond with an increase in the rate of respiration that may amount to several times the normal (Plate 2, Figs. 4, 5 and 6). This increased rate is characterized by a decrease in the duration of the expiratory pause and may occur with or without a change in the amplitude of the respiratory excursions. In an apparently normally excitable cortex the degree of acceleration appears to depend to a certain extent upon the intensity of the stimulus. A limit, however, is reached beyond which no further increase in rate is obtainable. Acceleration in the monkey was never obtained to the same degree as in the cat and the dog. In the latter animals, under very light anesthesia, typical panting respirations were sometimes produced.

In all animals both the inhibitory and acceleratory areas are present in corresponding positions on both sides of the brain and bilateral stimulation is more effective than unilateral. Isolation of the inhibitory cortex of the anterior composite gyrus or the acceleratory cortex of the rostral part of the anterior sigmoid gyrus by an incision through all the cortical layers does not abolish the response, but undercutting these areas without isolation renders them unresponsive. The response, however, can be obtained by stimulation of the cut ends of the underlying fibers, subsequent to removal of the cortical areas.

The responses were elicitable after bilateral section of the phrenic nerves and the vago-sympathetic trunks. They were also obtained after section of the spinal cord below the origin of the phrenics, thus demonstrating that the inhibitory effect is mediated over both intercostal and phrenic nerves and in the absence of one set the other suffices. Section of the corpus callosum does not abolish the responsiveness of the areas in either hemisphere, and removal of one hemisphere does not seem to affect the responsiveness of the acceleratory and inhibitory cortex in the other.

Reversal of response was found to occur from two cortical regions in the cat. The gyrus proreus which usually produced a marked inhibition of breathing occasionally responded with acceleration and a small cortical area near the rostral end of the sulcus ectosylvius anterior responded with acceleration under very light anesthesia and with inhibition when the anesthesia was

deeper. From the remainder of the respiratory fields a reversal of response has not been encountered.

#### IV. OTHER RESPONSES OCCURRING SIMULTANEOUSLY WITH THE RESPIRATORY ALTERATIONS

In cortical stimulation experiments a single effect is not always obtained from stimulation of one area, and even those areas which appear to give a single discrete response probably are concerned with functions other than those indicated by the observable one. It is not surprising therefore in the face of the indicated plurality of functions in the cerebral cortex, that other responses are elicited simultaneously with those pertaining to respiration.

In the very lightly anesthetized cat stimulation of the gyrus proreus not only effects an inhibitory response upon breathing but provokes a striking effect upon certain somatic responses. Body and extremity movements spontaneously executed are immediately stopped, rigidly extended extremities relax, lashing of the tail disappears, and the hyperactive animal appears to become thoroughly inactive and calm, at least in so far as ordinarily observable activity is concerned. In this instance inhibition of breathing seems to be part of a generalized inhibitory effect produced by excitation of this part of the cortex. In the dog, however, similar inhibitory responses were not produced by stimulation of this gyrus. The generalized inhibition that occurs in the cat upon stimulation of the gyrus proreus, is also evident upon stimulation of most of the remainder of the respiratory inhibitory area.

In both the cat and dog, there may occur, simultaneously with the respiratory arrest, mastication, licking or swallowing movements, either singly or in combination, as a result of stimulation of the most excitable part of the inhibitory area in the gyrus compositus anterior; similar results are obtained as a result of excitation of the inhibitory area in the monkey. These accompanying effects are not obtained as a result of excitation of the more caudal part of the respiratory inhibitory field in the cat and dog. This latter observation combined with the fact that respiratory arrest or slowing can be obtained without the swallowing, chewing or licking movements, seems to exclude these processes as a cause of the inhibition of breathing produced by cortical stimulation.

Another frequent manifestation concomitant with the respiratory inhibition is that characterized by a marked rise in the arterial pressure with or without a decrease in the cardiac rate and an increase in the pulse pressure (Plate 2, Fig. 1). As regards this particular study the rise in arterial pressure must be seriously considered because it stimulates the carotid sinus and thus may produce respiratory changes reflexly (Heymans and Bouckaert, 1933). Although it is inconceivable that an increase in arterial pressure of the degree obtained in these experiments would suffice to arrest breathing, it is possible that such an increase might effect a reflex decrease in the rate of breathing. That the rise in arterial pressure is effected by a nervous mechanism independent of that producing respiratory inhibition is attested by the finding that the

arterial pressure increase does not always accompany the respiratory response and when it does occur increase in the depth of anesthesia abolishes the cardiovascular response but leaves intact the respiratory one. The crucial experiment, however, consisted in stimulation of the respiratory inhibitory area in the gyrus compositus after removal of both carotid sinuses and both carotid bodies. Under such conditions when carotid sinus effects are definitely excluded respiratory inhibition still occurred. The independence of the two processes is further established by the fact that the increase in arterial pressure is obtained from the inhibitory area in the gyrus compositus anterior when the animal is under artificial respiration after the respiratory movements have been paralyzed by curare (Plate 2, Fig. 8).

From the acceleratory area a marked fall in arterial pressure usually occurs simultaneously with the respiratory acceleration (Plate 2, Fig. 5). As is the case with inhibition the acceleratory effect is sometimes obtained without a change in the arterial pressure. In all three species the acceleratory phenomenon was usually accompanied by turning of the head and eyes toward the contralateral side, by bilateral dilatation of the pupils and by movement of the contralateral foreleg.

#### V. CYTOARCHITECTURE

The cytoarchitecture of the cortical region from which respiratory alterations were obtained is of interest from the point of view of the relation between structure and function, for in cat, dog and monkey, the acceleratory cortex is situated predominantly in the area frontalis agranularis (area 6 of Brodmann), more especially in the part of this area designated by C. and O. Vogt (1919) for the monkey as area 6a. In all three animals this cortex is characterized by an indistinct lamination, by a paucity of granular cells and by the absence of definite granular layers. In the cat and dog this area is relatively small as compared to the same area in the monkey and not so well differentiated. It is therefore not surprising to find that the acceleratory area in the cat and dog extends caudally into the transition zone between areas 4 and 6a and rostrally into the transition zone between area 6a and the poorly differentiated cortex of the gyrus proreus. This more or less gradual structural change between area 6a and the cortex of the gyrus proreus belies the abrupt physiological change which is evident upon electrical excitation, for the small vein that usually is found leaving the medial end of the sulcus praesylvius to enter the superior longitudinal sinus by passing across the junction of the gyrus proreus and the gyrus sigmoideus anterior often marks the rostral boundary of the acceleratory cortex. In many cats stimulation just caudal to this vein produced acceleration while stimulation just rostral to it produced inhibition. In a similar manner in both cat and dog a small vein passing from the rostral end of the coronal sulcus to the sulcus praesylvius often marked an abrupt change from acceleratory to inhibitory cortex. Thus far it has not been possible to correlate these sudden physiological changes with any abrupt cytoarchitectural transitions.

The inhibitory cortex in the cat and dog occupies a relatively large part of the cortical surface. In view of this it is not surprising to find that the region from which inhibition is obtained consists of several cytoarchitecturally different areas. However, the cortical area in the cat and dog from which inhibition is most easily elicited (that is, the area in the anterior composite gyrus) and the inhibitory area in the monkey consist of cortex similar to that described for the acceleratory area, but are cytoarchitecturally differentiated from it chiefly by the presence of a greater number of granular cells and by the indication of granular layers. This inhibitory area therefore belongs to the lateral part of area 6 and has been designated by C. and O. Vogt (1919) for the monkey as area 6b, the area frontalis dysgranularis. In the cat and dog the less powerful inhibitory cortex caudal to this area is distinctly granular in type, having definite granular layers.

The gyrus proreus from which an inhibitory response is usually obtained in the cat possesses, in its caudal part, cortex similar to that of area 6a, but this undergoes a gradual transition so that more rostrally this gyrus has what appears to be a rather undifferentiated type of cortex which Langworthy (1928) describes as having an embryonic appearance. In the dog no alterations of breathing were obtained from cortex of this type.

## VI. COMMENT

The evidence obtained in this investigation indicates that the premotor area (area 6) is primarily the one from which both acceleration and inhibition can be obtained by electrical stimulation. The fact that acceleration was usually obtained from excitation of the medial part of this area and inhibition from excitation of its lateral part lends further physiological evidence in support of the already made cytoarchitectural separation of area 6 into a medial part (area 6a) and a lateral part (area 6b). In no instance were respiratory alterations obtained from excitation of cortex which could be unmistakably identified as motor cortex (area 4). This finding therefore refutes the contention of Bochefontaine (1876) and François-Franck (1887) that alterations of breathing could only be elicited by stimulation of the sigmoid gyri in the cat and dog and that no relation exists between the point stimulated and the response elicited. Furthermore, the finding that the inhibitory cortex of the anterior composite gyrus in both cat and dog appears to belong cytoarchitecturally to area 6 is not in agreement with Brodmann's (1906) concept of the structure of this region, for in the cat he designated it as part of the agranular gigantopyramidal area (area 4). Also, in the dog the inhibitory cortex of the anterior composite gyrus was found to possess a structure which marks it as belonging to area 6b and not to area 4 as Klempin (1921) reported. The fact that the acceleratory cortex belongs to the frontal adversive field and that the inhibitory cortex of the anterior composite gyrus belongs to the area from which mastication and deglutition is elicited is also evidence against either area being homologous with area 4 of primates.

In the monkey (*Macaca mulatta*) the acceleratory area is situated in cor-

tex typical of area 6a and the inhibitory area in cortex typical of area 6b. C. and O. Vogt (1919) in *Cercopithecus* limited the respiratory inhibitory field chiefly to their area 6b $\beta$ , but the results of my investigations do not indicate such a fine distinction because all of area 6b was found to have an inhibitory effect.

Even though the gyrus proreus in both the cat and dog consists for the most part of undifferentiated cortex of a structurally similar type, the inhibitory effect elicited by stimulation of this gyrus in the cat was not found to occur in the dog even when strong stimuli were used. However, Polimanti (1906) reported inhibition of respiration from stimulation of this gyrus in the dog. Not only has this finding of Polimanti (1906) not been confirmed by this investigation but in addition, no evidence has been obtained to support the contention of Gianelli (1900) and others that separate cortical areas exist for the innervation of the inspiratory and expiratory muscles respectively.

That the cortex normally exerts an influence on panting in the cat and dog is suggested by the finding that respirations simulating panting can be produced by stimulation of the acceleratory area, and also by the fact that panting can be inhibited to the point of cessation by stimulation of the inhibitory area. Furthermore, Pinkston, Bard and Rioch (1934) found that after removal of the cerebral cortex in cats and dogs true polypneic panting was absent and in its stead a long delayed slow hyperpnea occurred under conditions which would have promptly produced panting of the usual type.

The course of the corticofugal impulses effecting respiratory alterations is not known, but the fact that such impulses are able to exert their influence through extrapyramidal pathways seems evident from the investigations of Tower (1936) who obtained alterations of breathing from cortical stimulation in the cat after section of both corticospinal tracts at the upper level of the pons. It is likely that the impulses set up by stimulation of the areas in either hemisphere exert their influence primarily upon the myelencephalic respiratory mechanism rather than directly upon the spinal motoneurons since the respiratory muscles appear to be affected bilaterally as a functional unit.

The cortical effect presumably may either increase the rate of discharge of the volleys of impulses from the myelencephalic "respiratory center" thus producing acceleration of breathing, or it may entirely prevent the discharge thus causing cessation, or it may increase or decrease the frequency of the impulses composing each volley thus producing either a respiration of greater or lesser amplitude, or the combinations of the above may occur so as to produce slowing or acceleration with increased or decreased amplitude.

#### SUMMARY

Alterations in breathing characterized by either inhibition or acceleration were produced by electrical stimulation of certain regions of the cerebral cortex in the cat, dog, and monkey (*Macaca mulatta*). In the cat and dog, under light ether anesthesia, an inhibitory effect upon breathing characterized by a temporary cessation or slowing was most easily elicited from an area in

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the gyrus compositus anterior. A less marked but definite inhibitory effect was obtained from most of the cortex of the sylvian and ectosylvian gyri, and in the cat from the gyrus proreus as well. Increase in the depth of anesthesia resulted in abolition of the response, the area in the anterior composite gyrus being the last to succumb. Stimulation of the inhibitory area not only slowed or arrested panting, but also abolished or prevented the alterations in breathing that are ordinarily produced by sensory stimulation.

The inhibitory area in the monkey is situated in the cortical field just caudal to the lower end of the sulcus precentralis inferior.

The acceleratory response was most easily elicited in the cat and dog from the rostro-lateral part of the anterior sigmoid gyrus and the adjacent cortex forming the caudal wall of the sulcus praesylvius, and in the monkey from stimulation of an area just rostral to the sulcus precentralis superior. In the cat and dog the acceleration at times was so great as to simulate panting, but in the monkey an increase in rate of such magnitude was never obtained.

Various types of somatic and autonomic responses were obtained simultaneously with the respiratory changes, but these have been excluded as possible causes of the respiratory alterations.

The region from which the acceleratory response was most easily elicited belongs cytoarchitecturally to area 6a in all three animals; that from which the inhibitory response was most easily obtained belongs to area 6b.

The presence in the cat, dog, and monkey of cortical areas possessing similar cytoarchitectural structure and yielding similar physiological responses, suggests the existence of a fundamental plan for the cortical control of respiration in the general scheme of cerebral cortical evolution.

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# FUNCTIONAL ORGANIZATION IN THE SENSORY CORTEX OF THE MONKEY (*MACACA MULATTA*)\*

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## INTRODUCTION

IN 1924<sup>5,6</sup> the location and extent of the sensory cortex were established in the brain of the monkey (*Macaca*) by means of the method of local strychninization. This cortex was found to occupy a large portion of the post- and precentral region, and to comprise three major subdivisions (the leg-, arm- and face-subdivisions). This mapping was achieved by the local application of minute quantities of strychnine to very small portions of the cortex; such applications, if performed within the sensory cortex, resulting in marked symptoms of sensory excitation (paraesthesiae, hyperaesthesia and hyperalgesia) in different parts of the body.

Such an application of strychnine not only produces symptoms of hypersensitivity but also typical changes in the electrocorticogram (ECG.),† namely the appearance of large, rapid potential fluctuations—"strychnine-spikes." The occurrence of such spikes is not limited to the sensory cortex; they appear upon local strychninization of any portion of the cerebral cortex. The distribution of the spikes, however, is dissimilar when the areas are dissimilar.

It is first of all with these dissimilarities in distribution that the present paper deals, both in regard to the distribution of the spikes within the cytoarchitectonic area, of which a part has been strychninized, and in regard to the distribution of the spikes in architectonic areas other than the area locally strychninized. Furthermore this paper deals with the observation that strychninization of two definite areas results, besides producing strychnine-spikes in other areas, in a temporary suppression of the electrical activity of another area. Finally the results obtained with strychninization were corroborated in experiments with electrical stimulation of various areas and recording of the electrical after-discharge in other areas.

## METHODS

The experiments were all performed on monkeys (*Macaca mulatta*), either fully anesthetized with Dial‡ (0.45 cc. per kilogram, half of the dose given intraperitoneally, half intramuscularly), or ether, or operated upon under

\* The expenses of this investigation were defrayed by a grant from the Fluid Research Funds of the Yale University School of Medicine.

† Although realizing the hybrid origin of this word, we wish to use the term to designate conveniently the record of the electrical activity of the cortex taken directly from its exposed surface and to differentiate this record from the electroencephalogram (Berger), in which the electrical activity of the cortex is recorded indirectly, through the skull of the subject, or at least not directly from the cortex.

‡ We wish to thank the Ciba Company for kindly putting the Dial at our disposal.

Vinylether\* and curarized, but studied while awake. The strychnine (3 per cent solution, colored with toluidine blue) was always applied to a very small portion of the cortex, measuring only 1-4 square mm., either by touching the cortex at the desired locus with a pledget of cotton wool twisted around the ends of an irisforceps and moistened with the strychnine solution or by covering the cortex with a very small piece of filter paper, soaked with the strychnine solution. Before application of the pledget or filter paper the excess strychnine solution was carefully removed from it. For brevity we will refer to the application of strychnine to a few square millimeters of cortex, by either procedure, as "local strychninization."

The electrocorticograms were taken from various portions of the cortex with two fine Ag-AgCl electrodes, 3 to 4 mm. apart, this being the optimal distance for recording the ECG. with this type of electrodes. In most of the experiments the electrical activity was recorded with a cathode ray oscillograph after suitable amplification through a two-stage DC-amplifier. This method permits only successive electrocorticograms. Later AC-amplification with a four-element Westinghouse oscillograph was used for simultaneous recording of four electrocorticograms. The results of these experiments confirmed the previous observations. In many experiments bipolar electrical stimulation of one cortical focus was performed and the changes in the electrocorticograms (electrical after-discharge) of various foci examined.

## RESULTS

In Figure 1 is shown the location and extent of the sensory cortex of the brain of *Macaca mulatta*, with the subdivision into its leg- arm-, and face-areas.<sup>5</sup>

It should be pointed out that, apart from the incorporation of the cytoarchitectonic denominations, the present diagram differs in two respects from that of 1924, namely in the relation of the beginning and end of the sulcus interparietalis to the various subdivisions. The diagram of 1924 was based upon the study of 20 monkeys, in which only a few experiments could be devoted to the areas in question. The present diagram is based upon a large number of experiments and represents more truly an "average" of the findings in relation to the configuration of the surface of the macaca's brain, which differs so much from animal to animal.

Within each subdivision are also represented some of its cytoarchitectonic areas, simplified and modified after the investigations of Brodmann<sup>1,2</sup> and C. and O. Vogt.<sup>3</sup> The main deviation from their diagrams is the inclusion in Figure 1 of a field 4-s between 4 and 6a. From our diagram it can be readily understood what is meant in this paper by local strychninization within arm 4 area (A.4), leg 6a area (L.6a), or face 2 area (F.2), etc.

### 1. Changes of the ECG. in general following local strychninization.

Local strychninization of any portion of the cerebral cortex elicits typical changes in the ECG. at the site of strychninization, namely the appearance of "strychnine-spikes." The first alteration, within a few seconds after the application of the strychnine, is an augmentation of the general electrical

\* The Vinylether (Vinethene) was kindly put at our disposal by the Merck Company.

activity of the cortex; 30 to 60 secs. later the strychnine-spikes begin to appear which are fully developed in about 2 to 3 minutes. With the development of the spikes the "background"-activity, i.e. the potential fluctuations between the spikes, often markedly diminishes. At the end of about 15 minutes, the spikes begin to decrease slowly in size and frequency, while the background-activity is returning to its original magnitude. In 20 to 40 minutes the ECG. has usually regained its original characteristics. Renewed local application of strychnine then reinduces the whole train of events.

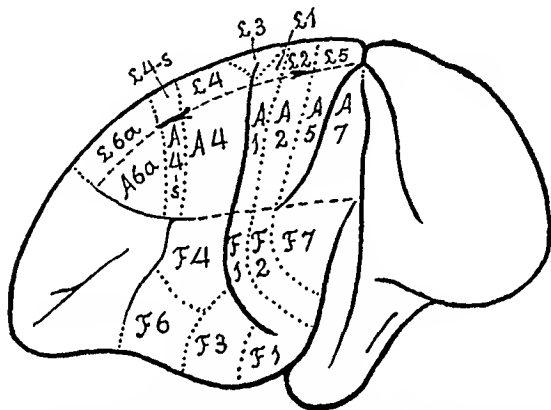


FIG. 1. Extent and location of the sensory cortex in the brain of *Macaca mulatta*, with some of the architectonic areas, appearing on the surface of the brain (slightly modified after Brodmann and C. and O. Vogt). The essential deviation from their diagrams is the introduction of an area L.4-s and A.4-s.

The configuration of the strychnine-spikes, recorded from the surface of the hemisphere, depends upon a number of factors, of which the most important are the size and positions of the electrodes and the stage of strychninization. We cannot enter here into a discussion of these relations; they have been dealt with to some extent at the Atlantic City meeting of the American Neurological Association, June, 1937 (See Transactions of that meeting).

Local strychninization anywhere within the *sensory* cortex (see Figure 1) produces spikes not only in the ECG. of the minute area strychninized, but also in other portions of the sensory cortex. The distribution of these spikes is wide-spread, but not fortuitous. It is constant for any given area, but different for the various cytoarchitectonic areas and the various major subdivisions of the sensory cortex. This distribution is altered neither by deep undercutting of the whole sensory cortex, nor by thermocoagulation of a narrow circular strip of cortex, throughout its entire thickness, around the area strychninized.

## 2. Distribution of the strychnine-spikes within the area locally strychninized.

The distribution of the spikes within an area locally strychninized differs for various regions of the cerebral cortex. This distribution is very restricted within the visual cortex (area 17 of Brodmann) and within area 5 of the sensory cortex: large spikes are present at the site of strychninization, small spikes in its immediate vicinity. One or two millimeters and farther away from the strychninized locus spikes are absent (see Figure 2).

In other portions of the cerebral cortex the distribution of the strychnine-spikes is much wider. Local strychninization of A.4 for instance results in a "firing" of the whole of this area, i.e., results in the appearance of spikes in the ECG. of all of A.4 (see Figure 3).

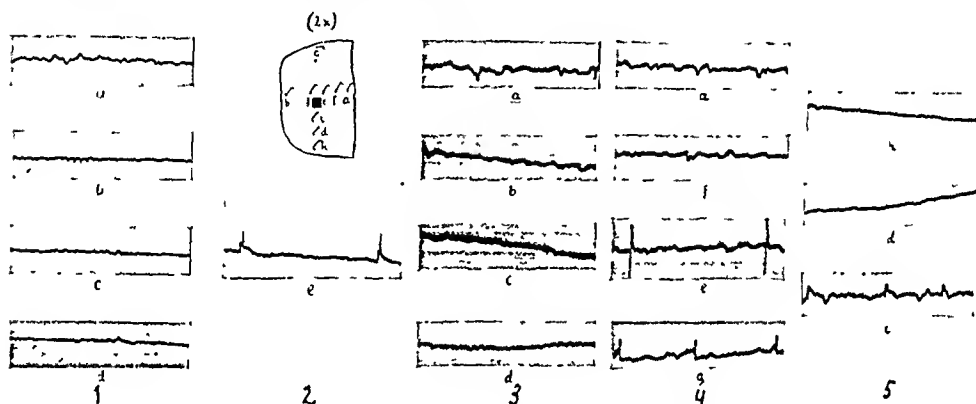


FIG. 2. Figure 2 gives the results of local strychninization of the visual cortex (area 17 of Brodmann) and shows that the strychnine-spikes appear only in the immediate vicinity of the strychninized area. First column shows the ECGs before the strychninization. The other ECGs of the loci indicated by the letterings at different times after the strychninization. Same amplification throughout. Column 1 before, the other columns after the strychninization. ECG. of column 2 (e) taken 2 minutes after, those of column 3, 4 minutes; column 4, 7 minutes and column 5, 10 minutes after the strychninization.

## 3. Distribution of the strychnine-spikes in other areas than the one strychninized.

One finds the widest distribution of the strychnine-spikes in the sensory cortex. The local strychninization of any cytoarchitectonic area within this cortex produces spikes in several other constituent areas. It is advisable to take up the various subdivisions of the sensory cortex separately. We shall first describe the findings relating to the arm-subdivision. Here the following results obtain: local strychninization of area 7 "fires" not only this area itself, but also areas 5, 2, 1 and 4; that of area 5 "fires" areas 2, 1 and 4; that of area 2 "fires" also areas 7, 5 and 4; that of area 1 "fires" also areas 7, 5 and 2; that of area 4 "fires" also areas 7, 5, 2 and 1.

In the case of the leg-subdivision the same results are found so far as the homologous areas, mentioned for the arm-subdivision, are concerned. In the leg-subdivision a portion of area 3 appears on the surface of the hemisphere, so that there this area can be locally strychninized on its surface. Such

strychninization results in a "firing" of areas L 5, L.2, L.1, L.3 itself, and L.4. In the face-subdivision it was found that local strychninization of its post-central region "fires" this region and also the precentral portion, and vice-versa. As yet we have not enough experimental data to make a more detailed statement for this subdivision.

What is common to all of these cases is: (1) that strychnine-spikes are always largest in the area strychninized locally, and diminish in size with increase of distance of the area "set on fire" from the area strychninized; (2) that the distribution of the spikes is limited to the subdivision locally strychninized; and finally (3) that area 6a is not "fired."

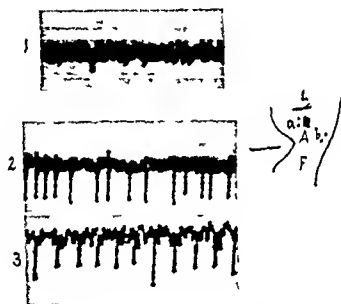


FIG 3 Figure 3 shows that local strychninization of A 4 is followed by large spikes throughout this area. Record 1 is ECG before strychnine-application. Record 2 gives the ECG at *a*, record 3 the ECG at *b* at the acme of the strychnine-spikes.

Figure 4 shows: (1) that local strychninization of A.5 does not "fire" this area, even in the vicinity of the locus strychninized; (2) that it "fires" A.4; (3) that it does not "fire" the precentral and postcentral region of the face- and leg-subdivisions. Figure 5 shows: (1) that local strychninization of L.4 "fires" L.4, L.2 and L.5; (2) that the spikes diminish in size the farther away the area "fired" is from L.4; (3) that the arm-subdivision is not "fired" and (4) that L 6a is not "fired."

In both Figures 4 and 5 the gradual return toward the normal ECG., present before the local strychninization, can be observed.

The sensory cortex situated in front of L.4 and A.4 requires separate mention. Here two areas, designated 6a and 4-s in Figure 1, can be differentiated.

First of all it should be stated that area 6a is the only portion of the sensory cortex which is not fired by the local strychninization of any other portion of the sensory cortex. Secondly, the local strychninization of either portion of

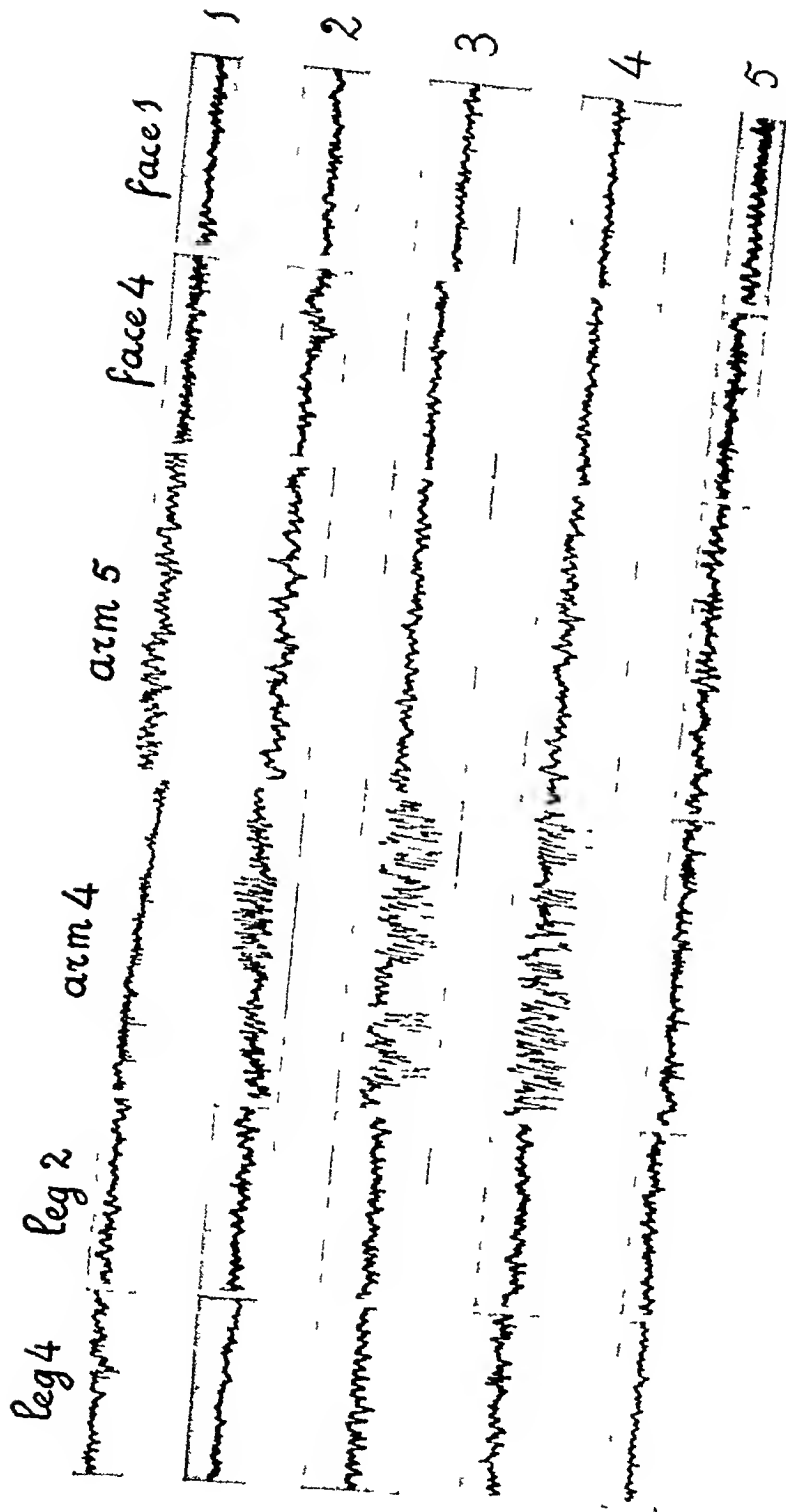


FIG. 4. Figure 4 (experiment of April 10, 1936; Dial-narcosis) shows the results of local strychninization of A.5. No apparent changes in the ECG. of A.5 immediately outside of the strychninized area. Enormous increase of the electrical activity in A.4. No changes in the ECG. of L.2, L.4, F.1 (and F.2) and F.4 (functional boundaries between the three major subdivisions). Row 1 gives the ECGs of A.4 in row 5.

area 6a, of L.6a or of A.6a "fires" all constituent areas of the leg- and of the arm-subdivisions, i.e. strychnine-spikes appear in L.6a, L.4, L.3, L.1, L.2, L.5, A.6a, A.4, A.1, A.2, A.5 and A.7.

The local strychninization of area 4-s produced equally striking results. Strychnine-spikes appeared in all of area 4-s, irrespective of the locus of strychninization in this area, i.e. in either A.4-s or L.4-s, and in the post-central portions of the arm- and of the leg-subdivisions. The new observation in this set of experiments was that a temporary *suppression* of the electrical activity of area 4 ensued, both in L.4 and in A.4. See Figure 6. Within a few minutes after the application of the strychnine to either L.4-s or A.4-s the electrical activity of L.4 and A.4 diminished considerably, while strychnine-spikes were present in the electrocorticograms of all the postcentral areas of the leg- and of the arm-subdivisions. After about 15 minutes, when the strychnine-spikes in these areas began to diminish in size and frequency, the ECG. in area 4-s began to come back and 20 to 25 minutes after the application had returned to its normal magnitude, simultaneously with the disappearance of the strychnine-spikes in the other portions of the leg- and arm-subdivisions. No changes were apparent in the ECG. of area 6a. This result is shown in Figure 6.

Areas 6a and 4-s have, therefore, this in common that no functional boundary between the arm- and leg-subdivisions is apparent so far as the changes in the ECG. following local strychninization of these areas is concerned, both in regard to the distribution of the strychnine-spikes and in the case of area 4-s to the temporary suppression of the electrical activity of area 4.

The local strychninization of area 1, like that of area 4-s, suppresses temporarily the electrical activity of area 4, while "firing" the other postcentral areas of the sensory cortex; it does not produce any changes in the ECG. of area 6a. In the case of the local strychninization of area 1, however, these changes in the ECG. are restricted to the subdivision to which the minute strychninized portion of area 1 belongs. The results of the local strychninization of area 1 are shown in Figure 7.

#### *4. Electrical stimulation of one locus producing electrical after-discharge in other loci of the sensory cortex.*

From previous work<sup>8</sup> we knew that electrical stimulation of such a type (sufficiently long duration, long pulses, etc.) that when applied to the "motor" cortex motor after-discharge occurs, will at lower voltages still produce an electrical after-discharge, evidenced in the ECG., though no peripheral motor response is manifest. We have found that when any focus of the sensory cortex is thus stimulated the electrical after-discharge is present not only at the site of stimulation and its immediate vicinity, but also at other foci, in other areas of this cortex. Thus we have here a method to check the results obtained in the strychnine experiments.

It was found that the distribution of this after-discharge upon appropriate



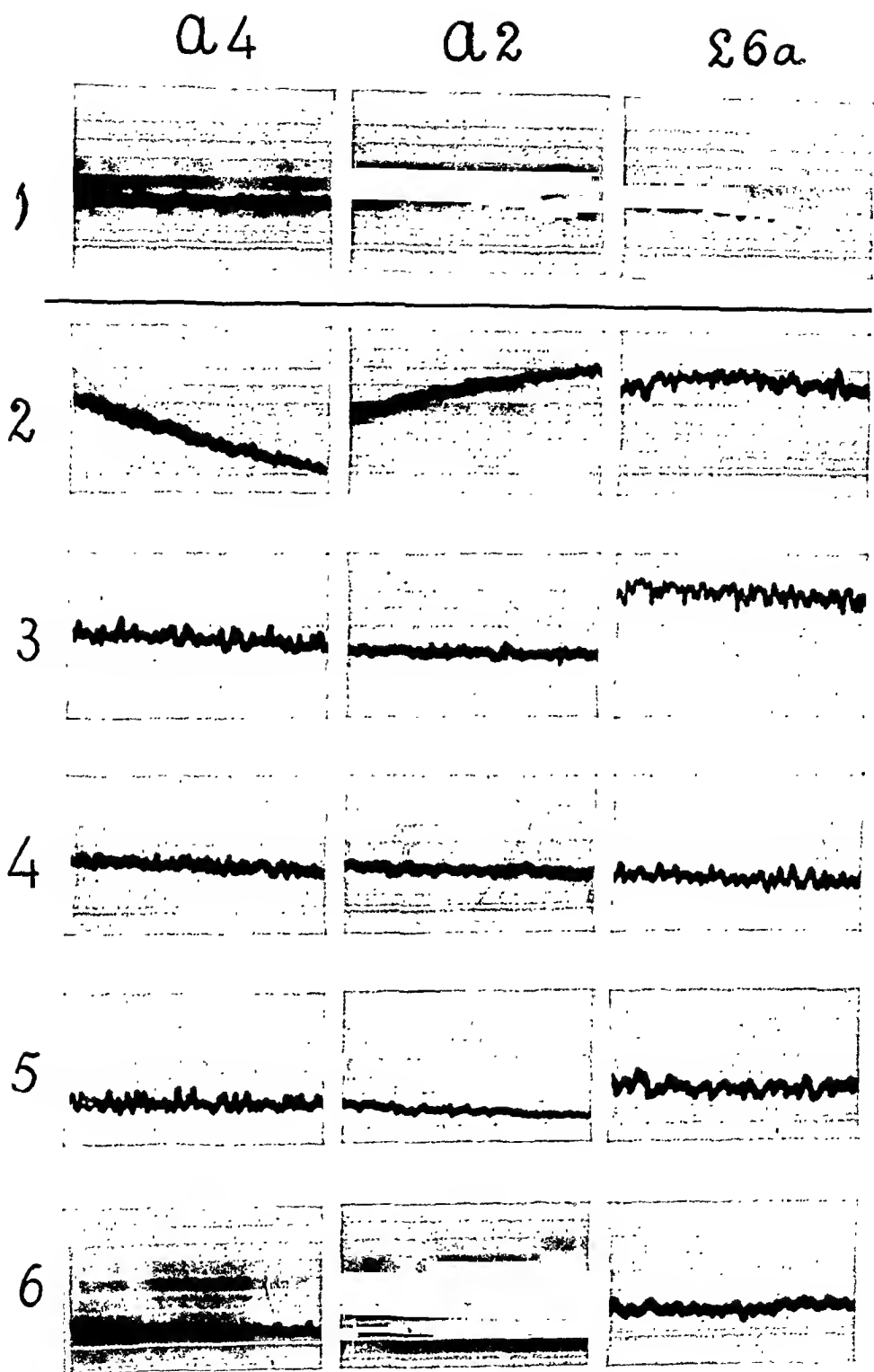
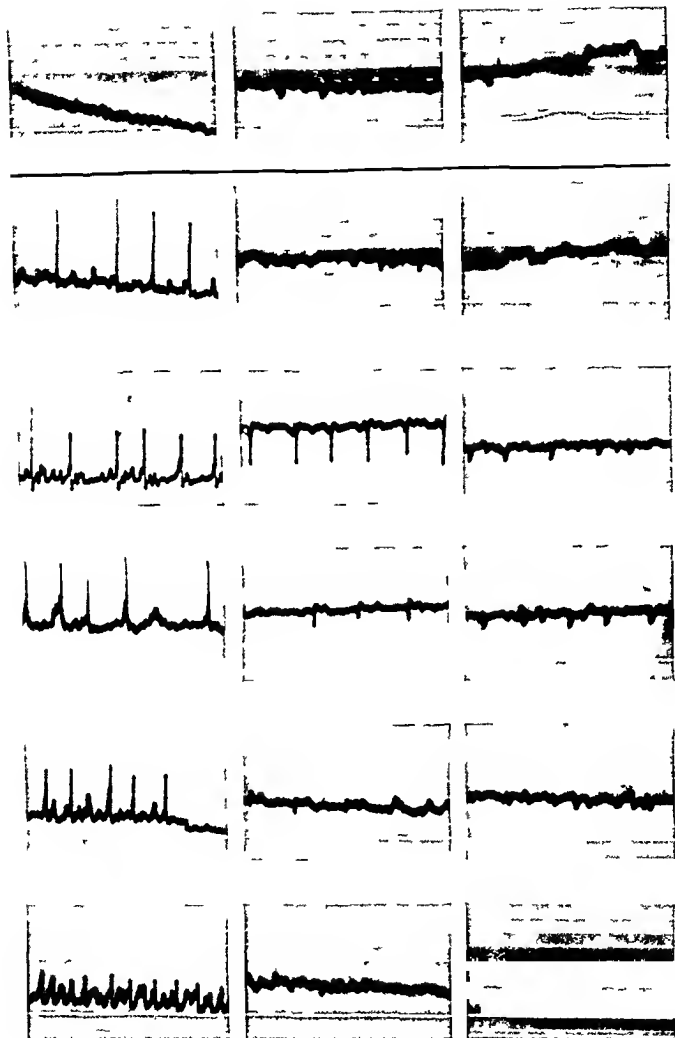


FIG. 5. Experiment of April 23, 1936. Dial-narcosis. Local strychninization of L.4 L.6a, nor in ECGs of A.4 and A.2. Row 1 before, the other rows after the strychninization. gradual return to "normal" from row 4 on.

L4

L2

L5



results in strychnine spikes in ECG of L4, L2, L5. No apparent change in ECG of Time interval between taking of the first ECG of each row ca 5 minutes. Note also the

electrical stimulation of any one locus of the sensory cortex was essentially the same as the distribution of the strychnine-spikes following local strychninization of this same locus. For this reason it is unnecessary to give the results of these experiments in detail.

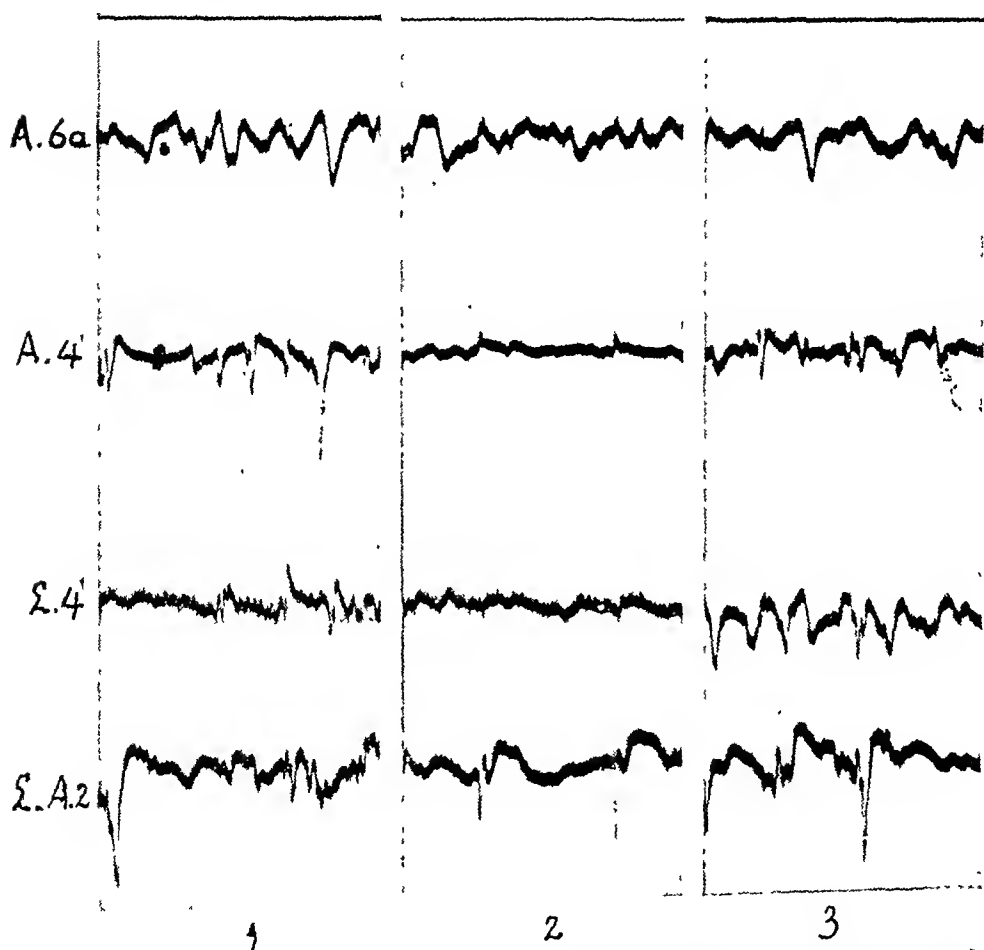


FIG. 6. Figure 6 shows in column 2 the temporary suppression of the ECG. of A.4 and L.4 upon local strychninization of A.4-s. Spikes in postcentral cortex (L-A.2 means that one of the two electrodes was on L.2, the other on A.2). No apparent change in ECG. of A.6a. Records of column 1 before, those of column 2, 7 minutes, and those of column 3, 11½ minutes after the strychninization of A.4-s. Simultaneous ECGs with 4-element Westinghouse oscillograph.

In Figure 8, which shows the distribution of electrical after-discharge in the leg-subdivision of the sensory cortex following appropriate electrical stimulation of a focus of L.4 (4.5 Volt, 5", 60~) it will be seen that electrical stimulation of a focus of L.4 produces electrical after-discharge in L.4, L.2, and L.5, but not in L.6a. Comparison with Figure 5 shows the similarity of the

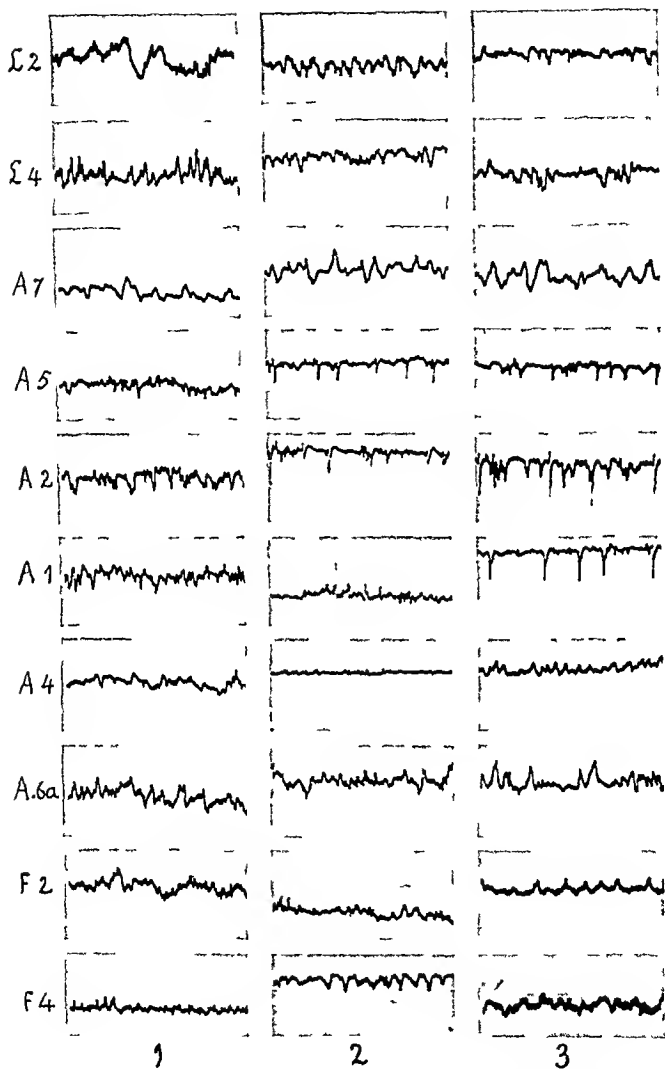


FIG 7 Figure 7 shows the effect of local strychninization of A1 Spikes in A1, A2, A5 Temporary suppression of ECG of A4 in column 2 No changes in A6a, nor in L2, L4, F2 and F4 Return to normal of ECG of A4 in column 3 Records of column 1 before, those of columns 2 and 3 after the strychninization

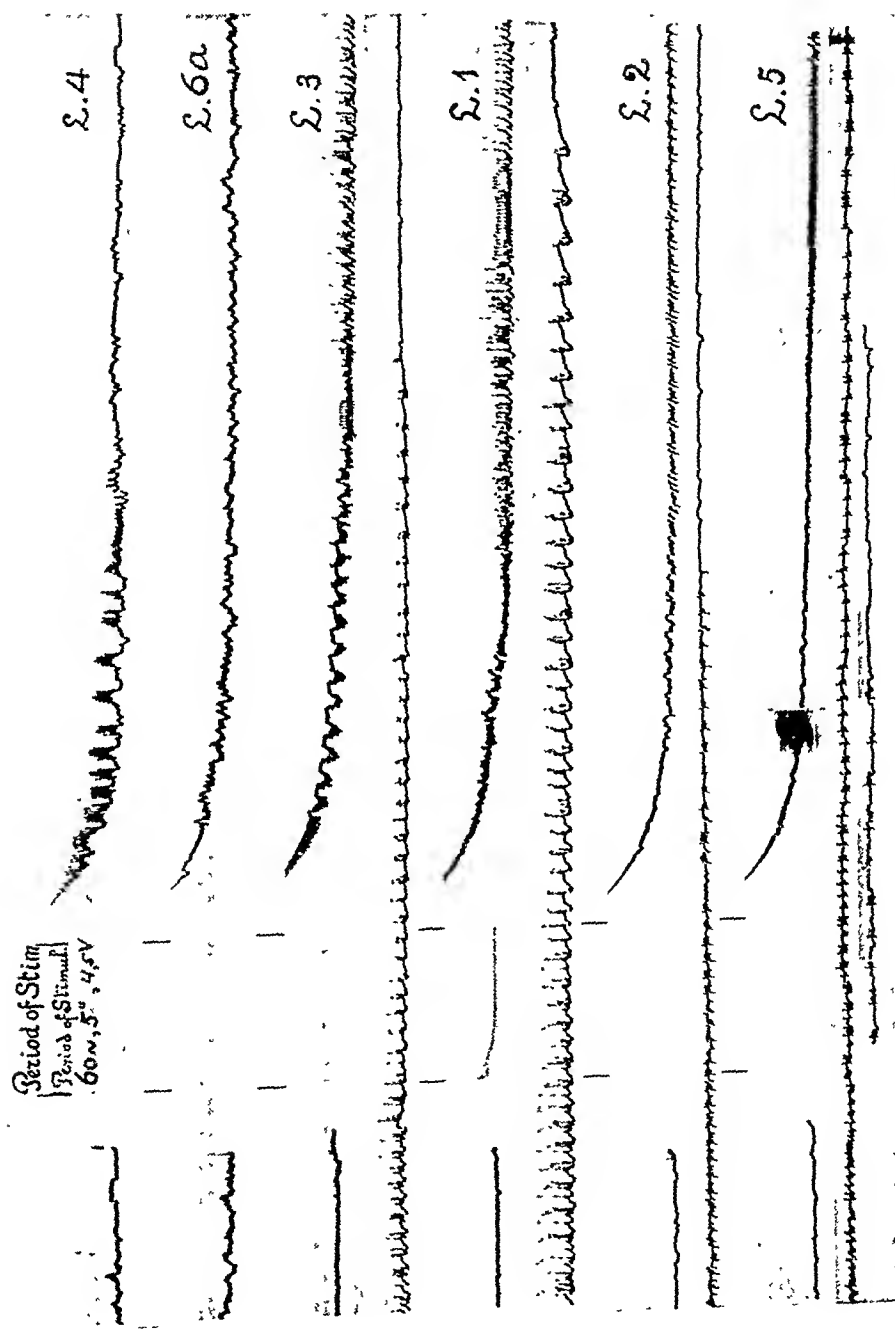


FIG. 8. Experiment of April 23, 1936 on same animal and same foci as of Figure 5. All records taken before and after electrical stimulation (60~, 4.5 V, 4 seconds) of a focus of L.4. Record 1 is ECG. of L.4 itself, 2 that of L.6a, 3 of L.3, 4 of L.1, 5 of L.2, 6 of L.5. Note electrical after-discharge in all records, except in that of L.6a.

distribution of the electrical after-discharge and the strychnine-spikes in these two sets of experiments, obtained by electrical stimulation and local strychninization of one and the same focus, with recording of the ECG. from the same loci in the same cortex of the same animal.

### DISCUSSION

The expression that local strychninization of one area "fires," or "sets on fire," this or another area is used purely for convenience to indicate the appearance of strychnine-spikes in this or that area. In 1912 one of us<sup>3</sup> adduced evidence indicating that strychnine produces its remarkable symptoms of sensory excitation, if applied locally to the dorsal horn of the spinal cord, by acting on the nerve cell bodies—the perikarya—within the strychninized area. It is plausible that this holds also for the cerebral cortex, both in regard to the symptoms of sensory excitation and to the typical changes in the ECG. following local strychninization of the (sensory) cortex.

The observation that injection of strychnine into the white matter underneath the cortex—the corona radiata—does not produce sensory symptoms nor strychnine-spikes in the cortex (or the thalamus) is experimental evidence supporting the view that the strychnine produces its remarkable symptoms by action on nerve cell bodies. The fact that essentially similar spikes occur at the site of strychninization irrespective of the cytoarchitectonic structure of the area in question shows that the local functional change induced by the strychnine is uniform throughout the cortex and that the spikes cannot be attributed to the strychninization of any single type of nerve cell. The specific distribution of the spikes encountered in these experiments for any given area strychninized precludes explanation of the findings in terms of any diffusion or absorption of the strychnine. This is in agreement with the older observations, previously adduced by one of us, which all indicate the remarkably local action of strychnine, when applied locally.

When strychnine-spikes appear in various areas upon strychninization within one area these distant spikes are practically simultaneous with the spikes in the area strychninized. Recording on fast-moving film or paper, however, shows that there is a delay of a few sigmas, the longer the greater the distance between the area strychninized and the area from which the spikes are recorded. Whether these propagated, distant spikes are merely axonal action-potentials or whether they reflect also the activity of nerve cells excited by these axons, is not settled. The long duration of the last phase of most of the spikes would seem to indicate that they can not be regarded entirely as pure axonal potentials.

Whatever the explanation of the strychnine-spikes may be, the fact that an area *a* "fires" an area *b*, whereas *b* does not "fire" *a*, must be the expression of *directed* functional relations, and, therefore, directed anatomical relations, between these two areas. Assuming that strychnine produces the spikes by acting on the perikarya of the cortex, the finding mentioned above must be interpreted to mean that nerve cell bodies in area *a* send their axons into area *b*, whereas *b* has no cell bodies the axons of which extend into *a*.

It is possible to make a few general statements about the course of these interareal axons. The distribution of the spikes is not changed by the thermo-coagulation of a narrow circular strip of cortex over the entire thickness of the cortex around the strychninized locus nor by deep undercutting of the whole sensori-motor cortex. These findings prove that axons from the area strychninized run through the white matter of the pallium to those other areas in which strychnine-spikes are present. Even within one area, e.g. A.4, circum-thermo-coagulation of the locus strychninized does not prevent spikes from appearing throughout that area, so that intraareal as well as interareal axons pass through the subjacent white matter. Obviously, these findings do not preclude the operation of intracortical, i.e. intragriseal, axons, but they do show that such axons are not necessary for the apparently normal distribu-

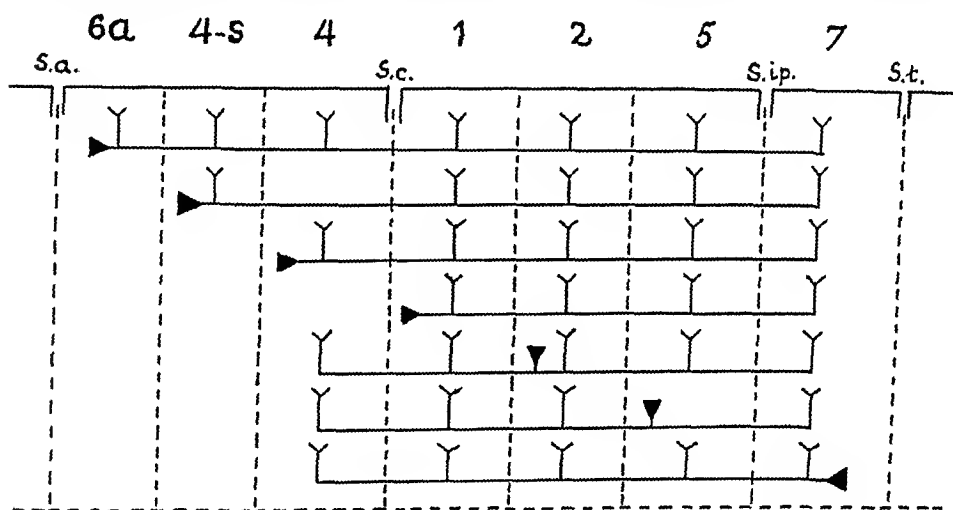


FIG. 9. In Figure 9 are represented diagrammatically the directed functional (and anatomical) relations between the various cortical areas of the arm-subdivision of the sensory cortex found in these experiments. The suppression of the ECG. of area 4 upon local strychninization of area 4-s or area 1 is not represented, because this is not dependent upon cortico-cortical relations.

s.a. = sulcus arcuatus; s.c. = sulcus centralis; s.i.p. = sulcus interparietalis; s.t. = sulcus temporalis I.

tion of the strychnine spikes. The specific intraareal and interareal, directed functional relations within the sensory cortex, schematised on the basis of the view that strychnine produces spikes by action on the perikaryon, are given diagrammatically in Figure 9. For reasons of simplicity, the axons are drawn as remaining inside the "griseum" of the cortex, although, as stated in the preceding paragraph, they actually run through the subjacent white matter.

The feature common in the phenomena observable after local strychninization of 6a or 4-s is the appearance of strychnine-spikes in both leg- and arm-subdivisions of the sensory cortex, although the strychninization was performed in only one of the following areas: either L.6a or A.6a, L.4-s or A.4-s.

This means that, so far as the appearance of strychnine-spikes in the ECG. upon local strychninization of these areas is concerned, no functional boundary between the leg- and arm-subdivisions exhibits itself. Furthermore the local strychninization of either L.4-s or A.4-s results, as shown, in a suppression of the ECG. of L.4 and A.4; thus, in this respect, also no boundary appears. These findings contrast with the functional boundaries between these subdivisions of the sensory cortex as they manifested themselves by the distribution of the symptoms of sensory excitation in the experiments on the monkey by one of us in 1924.

This contrast, however, is not a contradiction. The ECG. expresses the activity of the cortex at that level of the CNS, the hypersensitivity depends also upon lower levels, notably the optic thalamus. Experiments in which the electrical activity of the thalamus, the electrothalamogram, was recorded before and after local strychninization of the sensory cortex have provided a satisfactory explanation for the apparent discrepancy mentioned above. The full discussion of this problem must, however, be reserved for a subsequent paper, which deals with the functional interrelation of the sensory cortex and the thalamus.

Our area 4-s lies as a narrow band of cortex in front of L.4 and A.4. The occipital border usually runs from the posterior end of the arcuate sulcus through the posterior portion of the superior precentral sulcus, and continues almost parallel to the central sulcus onto the medial aspect of the hemisphere. This border, however, is more or less arbitrary because of the great variability in size, form and direction of the superior precentral sulcus and of the arcuate sulcus. For the anterior border of area 4-s there is no landmark on the surface of the hemisphere. All we can say on the basis of our physiological observations is that area 4-s is a narrow band of cortex, the width of which measures ca. 2 mm. at its bottom and 3 to 4 mm. at its top.

It should be pointed out that extent and location of area 4-s, as given in Figure 1, should be regarded as an "average" of numerous experiments.

The variability in the pattern of the sulci of the hemisphere of *Macaca mulatta* (and other species) is so great that the location of area 4-s can only be "diagnosed" experimentally. This leads in many experiments to interesting composite, additive results. If the strychnine is applied not strictly within area 4-s, but encroaches upon area 4, this will show up as a combination of a suppression of the ECG. in L.4 and A.4, the part of the symptomatology due to the strychninization of 4-s, with occasional, rather small spikes in L.4 or A.4, due to the strychninization of the most anterior part of this area. If the intended strychninization of area 4-s has been performed too much frontally, the most posterior portion of area 6a will also be involved. This will show up by the fact that together with the suppression of the ECG. in area 4, there will appear small spikes in L.4 and A.4 and large spikes in area 6a. Only if the strychninization has been performed "purely" in area 4-s will a "pure" suppression in L.4 and A.4 appear without any trace of spikes in these areas or in area 6a. In fact, we have in several animals performed such a series of differently located local strychninizations in this region, thus establishing the exact location and extent of area 4-s in each specimen. Usually area 4-s was found to lie more forward than expected on the basis of examination of the surface configuration, especially on brains in which a large posterior "spur" of the arcuate sulcus is present.

The resemblance in extent and location of area 4-s with the "strip" of



Marion Hines<sup>6</sup> is quite striking. Electrical stimulation of this strip of cortex in her hands abolished existing motor activities, extirpation resulted in spasticity, findings entirely in harmony with the temporary suppression of the ECG. of L.4 and A.4 upon local strychninization of area 4-s. There can be, therefore, no doubt that the "strip" of Hines is identical with our area 4-s. Dr. Hines has written us that she dislikes the colloquial designation of this area as "the strip," an expression having come into use as laboratory slang. The cytoarchitecture of this area, according to Dr. Hines, is similar to that of area 4, but can readily be distinguished from it by the great reduction in the number of Betz cells. It seems advisable and appropriate, therefore, to designate this area as area 4-s.

The cortex in front of area 4-s has the cytoarchitecture of area 6 of Brodmann. Dr. Hines wrote: "And if one is very fussy about cytoarchitecture this area 6 could be divided into two regions again. The pyramidal cells in layer III of the posterior part of area 6 are larger than those found in the same layer of the anterior part of this area." So far we have not been able to find any functional differentiation upon local strychninization of area 6a, and have, therefore, refrained from subdividing it.

If it be permissible to transpose the cortex of *Macaca mulatta* upon that of *cercopithecus* of the Vogts (species not given so far as we know) it is obvious that our areas 4-s and 6a are not to be identified with the areas 6a $\alpha$  and 6a $\beta$  of C. and O. Vogt.

The suppression of the ECG. of L.4 and A.4 by local strychninization of area 4-s is not brought about by cortico-cortical neurons. The experimental evidence upon which this statement rests, will be given in a subsequent paper. The observations presented in this paper confirm the hypothesis advanced by Dusser de Barenne in 1916 and again in 1924 to explain the finding that strychninization of a few square millimeters of the sensory cortex gives rise to symptoms of sensory excitation in a large portion of the body. At that time it was stated "as the most plausible explanation that the strychnine brings the small cortical area poisoned by it into a condition of abnormal and intense hyperexcitability and hyperactivity, and that this condition irradiates from the area poisoned over the whole of that part of the cortex which is in close functional connection with it" [(5) p. 285; see also (4) p. 383]. This assumption has now been proved to be correct in general. The present experiments have revealed details which have been dealt with in this paper.

The method of local strychninization with simple "clinical" observation of the animal failed to reveal functional differentiation within the sensory cortex except for the existence of functional boundaries between its major subdivisions, and, therefore, could not throw further light upon the problem of functional localization within the sensory cortex. The method of local strychninization was used in conjunction with recording of the ECG. with the definite anticipation that this combination of methods would uncover just such finer differences of functional organization in the sensory cortex; this expectation has been confirmed by the experiments presented in this paper. These observations have permitted amplification and specification of the original hypothesis.

## SUMMARY

1. The method of local strychninization in combination with that of recording the electrocorticogram (ECG.) has proved suitable for study of the problem of functional organization within the sensory cortex of the monkey.

2. Local strychninization of the cerebral cortex induces typical changes in the ECG, namely the temporary appearance of large and rapid potential fluctuations, or "strychnine-spikes."

3. The distribution of these spikes differs with the locus of strychninization. In the visual cortex (area 17 of Brodmann) and in area 5 of the sensory cortex they are restricted to the area strychninized and its immediate vicinity. In the sensory cortex the spikes are widespread and their distribution specific for different areas.

4. These specific differences in distribution, described in this paper, are the expression of directed relations between the various portions of the sensory cortex, of a functional organization within this region.

5. The local strychninization of two areas of the sensory cortex (areas 4-s and 1) results in a temporary suppression of the ECG. of areas L 4 and A.4, while "firing" other portions of the sensory cortex.

6. Experiments with recording of the ECG. and local electrical stimulation of various areas of the sensory cortex showed that the distribution of the propagated excitation, manifesting itself in the spread of an electrical after-discharge, was the same as the distribution of the spikes elicited by local strychninization of these same areas.

7. The observations reported here confirm and amplify the original hypothesis of one of us of an intimate functional interrelation of the various areas within any one major subdivision of the sensory cortex.

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the motor region.<sup>19</sup> The similarity in frequencies of tremor movement and brain potentials from the motor region, as compared to the alpha rhythm from the occipital region in subject E. R., is shown in Fig. 1-A. The groupings of muscle action potentials from the extensor and the flexor (sublimus) muscles of the digits in this subject also showed, at times, a 10 per second rhythm and a 25 per second rhythm corresponding to the two components of the tremor. Subject E. R. showed the same frequency of alpha rhythm from the motor and occipital regions corresponding also to the slow component of the tremor. In subjects who showed a difference between the occipital alpha and the motor alpha rhythm, the tremor showed a closer correspondence with potentials from the motor region. For example, in subject M. O. (Fig. 1B), the occipital alpha rhythm was about 9.5 per second while the

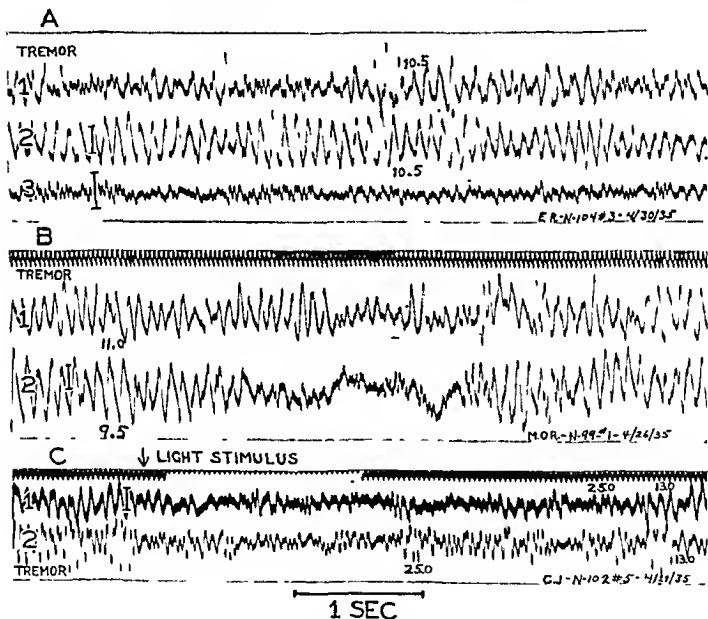


FIG. 1. Normal Tremor and Brain Potentials. A. Subject E. R. showing the slow (10.5 per sec.) and the rapid (25 per second) rhythm in the tremor from the right index finger (1) corresponding to the frequencies found in the Occipital (2) and precentral (3) brain potentials. B. Subject M. O. showing left index finger tremor at 11 per second (1) at the same time as occipital alpha rhythm (2) at 9.5 per second. C. Subject C. J. showing right precentral brain potentials (1) with left second finger tremor. The tremor shows the same frequencies and a similar response to light stimulation as the brain potentials.

rhythmic electrical disturbances, either spontaneously or in response to stimulation, which may be related in some way to excitatory processes which reach motor neurons innervating voluntary musculature.

It is the purpose of the present study to investigate further, in man, the relationship between rhythmic cortical potentials as recorded through the unopened skull and certain rhythmic characteristics of involuntary contraction in striate muscle. We have approached this problem through simultaneous records of normal brain potentials with records of normal finger tremor and muscle action potentials, in addition to studies of pathological tremor in paralysis agitans and the rhythmic clonic movements in relation to seizure waves in epilepsy.

#### TECHNIQUE

Four balanced completely push-pull, condenser coupled amplifiers leading to a four element Westinghouse oscillograph were used for independent recording from different head regions and for recording muscle potentials, tremor, and brain potentials simultaneously on continuous photographic recording paper. Muscle potentials were recorded either from concentric needle electrodes or from surface electrodes on the skin.

In order to obtain tremor movements with a minimum of distortion, one finger was held by the subject in a slightly extended position free from any mechanical attachments. The rest of the hand and fingers were held firmly in a frame. Two methods of recording were used, (1) a very light piece of metal was taped to the end of the finger which was placed in the magnetic field of a head-phone, the potentials set up in the phone coils being led to the input of the amplifier, and (2) the finger was placed in a wedge-shaped beam of light focused on a Weston photonic cell which was connected to the amplifier. Each of these recording devices was capable of detecting finger movements which were scarcely visible. The first method of recording exaggerated the more rapid components of the tremor to some extent so that it was abandoned in favor of the photo-cell recording for the majority of the experiments. The photo-cell method also eliminated the continuous down pull on the finger exerted by the magnetic field. The sensitivity of the tremor recording devices was adjusted so that there was no electrical interference with the amplifiers used for recording the brain and muscle potentials.

The technique used for the bipolar or monopolar records of brain potentials from electrodes on the scalp surface is similar to that described in previous publications (18, 19).

#### *Normal brain potentials and tremor movements*

Tremor movements of the fingers were found to have a major rhythm at frequencies between 8 and 13 per second in 10 normal subjects, with an average frequency of about 10 per second.\* A secondary tremor frequency between 17 and 30 per second was also present with an average of about 25 per second. These frequencies correspond very closely to the alpha and beta rhythms previously reported as characteristic of cortical potentials from over

\* In some subjects the average frequency from the little finger was 0.5 to 1.0 cycle per second slower than that from the index finger which showed that mechanical effects on tremor frequency were not without importance. Precautions were taken to limit the recording to only the vertical movements of one finger which avoided gross mechanical distortion from hand movements and the interference from the other digits. Under these conditions those subjects with a fairly large tremor showed the same frequency in each of the four fingers suggesting that the finger movements were representing actual muscle tension rhythms. This was confirmed in records of muscle potentials which showed groups of muscle potential discharges at the tremor frequencies as reported by Travis and Hunter (27, 28). We were not able to ascertain from our records of muscle potentials taken with needle electrodes, whether the grouping was made up of interrupted trains of unit discharges or volleys. The latter is more probable. Experiments are now in progress to elucidate this point.

# BRAIN POTENTIALS AND VOLUNTARY MUSCLE ACTIVITY IN MAN\*

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IT HAS long been known that the central grey matter possesses an inherent rhythmicity which is reflected in discharges along motor neurons to voluntary musculature. Horsley and Schafer, in 1886,<sup>16</sup> found that muscular contractions elicited by cortical stimulation in dogs, cats, rabbits and monkeys exhibited a rhythm independent of the frequency of stimulation. This rhythm, which they attributed to some fundamental property of the higher centers, was usually about 10 per second, or between 8 and 13 per second. Schäfer,<sup>26</sup> from records of muscle thickening during voluntary contraction in man, observed a rhythm of 8 to 13 per second with an average of 10 per second. This same frequency appears again in the early studies of the speed of single and repeated voluntary movements in man by von Kries (1886).<sup>21</sup> He found that voluntary rhythmic alterations of finger movement could not exceed about 10 per second.

Hoffman and Strughold<sup>15</sup> have recently shown that muscle action potentials in man in response to rhythmic stretching of the forearm at a frequency of 55 per second were not continuous, as might be expected from the simple "Eigenreflex." They observed rhythmic modulations in the amplitude of the train of action potentials. The major rhythm of this modulation, or interruption, occurred at a frequency of about 10 per second, demonstrating that the reflex centers in the cord were apparently undergoing a fluctuation in excitability at about this frequency.

According to Travis and Hunter,<sup>27 28</sup> the major tremor rate in normal individuals, as recorded from the end of the finger, is between 8 and 12 per second and is accompanied by rhythmic volleys or "envelopes" of muscle action potentials preceding slightly each tremor movement. A secondary rhythm of 40 to 50 per second was found to be superimposed upon the major 10 cycle frequency.

These results may have acquired a new significance in the light of Berger's discovery that the predominant potential rhythm of the cerebral cortex in man is also at about 10 per second, with a range of frequencies very similar to that found by Schafer in the super-imposed tremor during voluntary contraction in man. Cortical potential rhythms between 9 and 12 per second have also been found characteristic of cortical electrograms of the dog and the monkey.<sup>5 2</sup> Adrian<sup>3</sup> has recently demonstrated that certain potential waves from the motor cortex of the monkey are directly associated with excitatory processes to the motor neurons resulting in movements of the limb muscles. It appears from these studies that certain central neurons give rise to slow

\* Research conducted with the aid of a grant from the Rockefeller Foundation.

rhythmic electrical disturbances, either spontaneously or in response to stimulation, which may be related in some way to excitatory processes which reach motor neurons innervating voluntary musculature.

It is the purpose of the present study to investigate further, in man, the relationship between rhythmic cortical potentials as recorded through the unopened skull and certain rhythmic characteristics of involuntary contraction in striate muscle. We have approached this problem through simultaneous records of normal brain potentials with records of normal finger tremor and muscle action potentials, in addition to studies of pathological tremor in paralysis agitans and the rhythmic clonic movements in relation to seizure waves in epilepsy.

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#### *Normal brain potentials and tremor movements*

Tremor movements of the fingers were found to have a major rhythm at frequencies between 8 and 13 per second in 10 normal subjects, with an average frequency of about 10 per second.\* A secondary tremor frequency between 17 and 30 per second was also present with an average of about 25 per second. These frequencies correspond very closely to the alpha and beta rhythms previously reported as characteristic of cortical potentials from over

\* In some subjects the average frequency from the little finger was 0.5 to 1.0 cycle per second slower than that from the index finger which showed that mechanical effects on tremor frequency were not without importance. Precautions were taken to limit the recording to only the vertical movements of one finger which avoided gross mechanical distortion from hand movements and the interference from the other digits. Under these conditions those subjects with a fairly large tremor showed the same frequency in each of the four fingers suggesting that the finger movements were representing actual muscle tension rhythms. This was confirmed in records of muscle potentials which showed groups of muscle potential discharges at the tremor frequencies as reported by Travis and Hunter (27, 28). We were not able to ascertain from our records of muscle potentials taken with needle electrodes, whether the grouping was made up of interrupted trains of unit discharges or volleys. The latter is more probable. Experiments are now in progress to elucidate this point.

the motor region.<sup>19</sup> The similarity in frequencies of tremor movement and brain potentials from the motor region, as compared to the alpha rhythm from the occipital region in subject E. R., is shown in Fig. 1-A. The groupings of muscle action potentials from the extensor and the flexor (sublimus) muscles of the digits in this subject also showed, at times, a 10 per second rhythm and a 25 per second rhythm corresponding to the two components of the tremor. Subject E. R. showed the same frequency of alpha rhythm from the motor and occipital regions corresponding also to the slow component of the tremor. In subjects who showed a difference between the occipital alpha and the motor alpha rhythm, the tremor showed a closer correspondence with potentials from the motor region. For example, in subject M. O. (Fig. 1B), the occipital alpha rhythm was about 9.5 per second while the

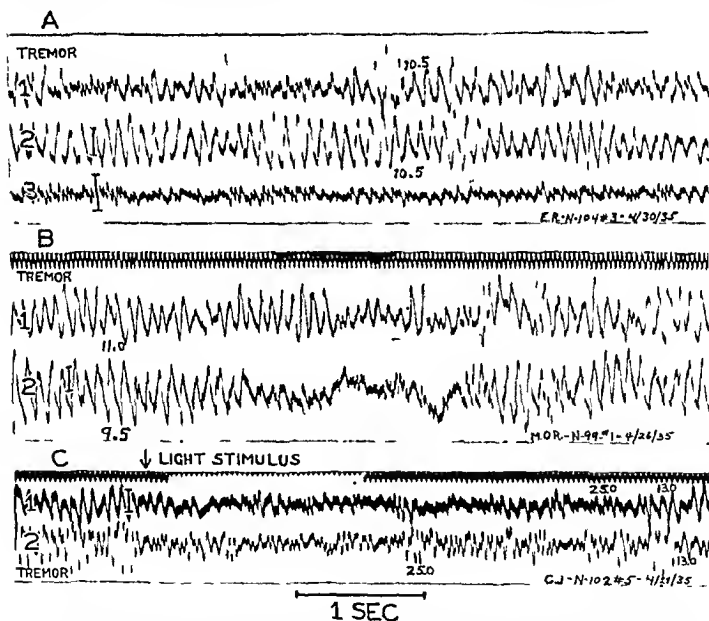


FIG. 1. Normal Tremor and Brain Potentials. A. Subject E. R. showing the slow (10.5 per sec.) and the rapid (25 per second) rhythm in the tremor from the right index finger (1) corresponding to the frequencies found in the Occipital (2) and precentral (3) brain potentials. B. Subject M. O. showing left index finger tremor at 11 per second (1) at the same time as occipital alpha rhythm (2) at 9.5 per second. C. Subject C. J. showing right precentral brain potentials (1) with left second finger tremor. The tremor shows the same frequencies and a similar response to light stimulation as the brain potentials.



slower components of the potential rhythms from the motor region were about 11 per second which corresponded with the tremor frequency.

The arrest of the occipital alpha rhythm, either "spontaneously" or by light stimulation of moderate intensity, may be associated with very little change in the tremor as shown in Fig. 1B. We have occasionally observed, however, changes in the finger tremor with unexpected auditory stimulation which parallel quite closely the changes in the potential rhythms from over the precentral region as shown in Fig. 1C. In some cases an unexpected auditory stimulus caused an arrest of the tremor for about one-half second followed by a sudden facilitation of the tremor to about twice its former magnitude, returning to its normal magnitude after about five seconds.\* The potentials from the motor cortex were usually decreased in magnitude during the period of augmentation of the tremor and returned to their normal amplitude and regularity as the tremor decreased to its normal level. In subjects with little or no slow rhythm from the motor cortex, as in the example given in Fig. 2C, no relationship can be shown between the brain potential rhythms and tremor frequency. Since the absence of the slow rhythms and the presence of low amplitude higher frequency potentials (40 to 60 per second) is characteristic of a condition of cortical excitation,<sup>17</sup> it seems that either the true frequency of cortical discharge is not obtained under these conditions, due to desynchronization, or the control of the tremor frequency is taken over by sub-cortical motor centers.

It appears from these results that tremor movements and brain potentials from over the precentral cortex may correspond closely in their frequencies and response to stimulation under certain conditions in normal individuals, but the absence of correspondence in other cases shows that there is no necessary relationship between the frequency of cortical potentials and that of the tremor movements.

#### *The effect of sleep on tremor and brain potentials*

Since brain potential rhythms are known to be altered markedly in sleep,<sup>13, 25</sup> it was thought that simultaneous records of tremor movements and brain potentials during sleep might help to clarify the functional relationship between these two phenomena.

Brain potentials from the frontal, precentral, and occipital regions of the head were recorded simultaneously with finger tremor movements during sleep in three normal individuals. In one of these individuals the tremor records during sleep were not sufficiently regular for consideration, due chiefly to technical difficulties. Examples of results from the other two subjects are given in Fig. 2. In subject H. C. the waking record (A) showed a relationship between the potentials from the frontal pairs of head electrodes (1 and 2) and the tremor from the right index finger (4) with a predominate frequency of 10 to 11 per second. The occipital alpha rhythm (3), however,

\* An augmentation of the alpha rhythm from the motor region is also occasionally observed in response to stimuli which causes a complete arrest of the alpha rhythm from the occipital region (19).

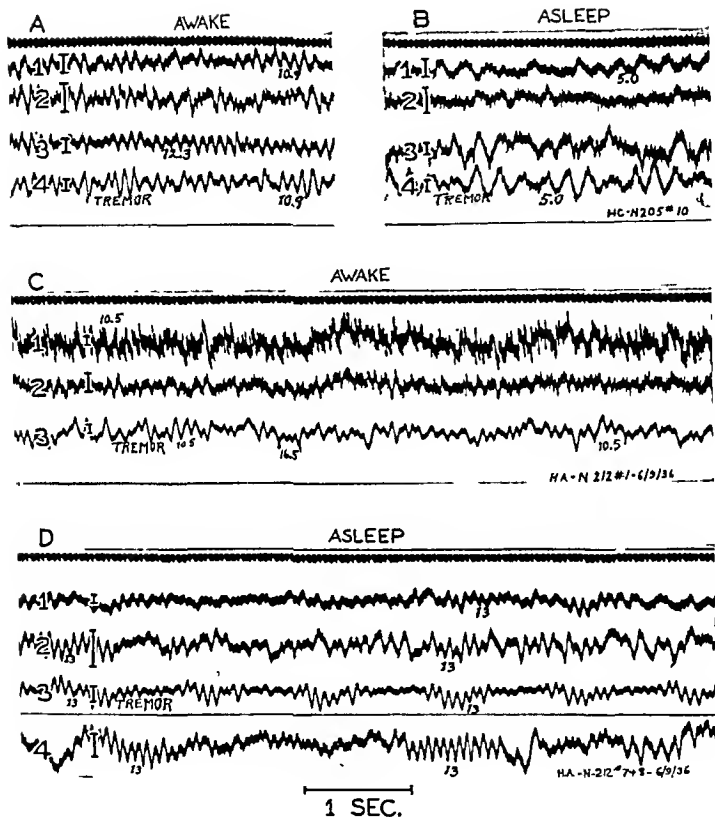


FIG. 2. Brain Potentials and Tremor During Sleep. The first records show correspondence between tremor frequencies from the right second finger (4) and brain potentials from the left frontal region (1) and lack of correspondence with occipital brain potentials from subject H. C. awake (A) and asleep (B). The second two records, from subject H. A. awake and asleep, shows little correspondence between either left precentral (1) or left occipital (2) brain potentials and right second finger tremor (3) awake but a remarkable correspondence between brain potential frequencies (1, 2, and 4) and tremor (3) during sleep.

was above 12 per second, showing little correspondence with the tremor rate. During sleep (B) both the tremor rate and the brain potential rhythms decreased to 5 per second. The second subject (H. A.) awake (C) showed little correspondence between tremor (3) and brain potential rhythms (1 and 2). (Former experiments on this subject had shown a much closer correspondence.) The tremor also was quite irregular showing possible frequencies at about 10 and 16 per second. During sleep, however, this subject showed a remarkable correspondence between tremor and brain potential rhythms with a characteristic frequency of 13 per second in each. This shows that the "sleep rhythm" or "spindles" of Loomis, Harvey and Hobart<sup>25</sup> may also be found in tremor movements. These changes in both tremor and brain potential frequencies as a result of sleep show a close functional relationship between cortical potential and tremor rhythms under these conditions.

One presumably normal subject, F. T., a female nurse 27 years of age, with no recognized neurological disorder, was selected for study because of a somewhat exaggerated regular tremor in both hands. Recording with the photoelectric cell method, it was found that the same frequency of tremor, 6 to 7 per second, was present in each finger of either hand. Placing the hand palm down or palm up and changing the amount of voluntary tension of the finger did not alter the tremor frequency. The brain potential rhythms from frontal, precentral, and occipital bipolar leads showed no correspondence with the tremor frequency at the beginning of the experiment as shown in Fig. 3A. The subject was nervous and apprehensive at this time and showed very little slow rhythm in the brain potentials from either bipolar or monopolar leads except for an occasional group of low amplitude occipital alpha potentials at a frequency of 9 to 10 per second. The tremor, however, was regular and continuous at a frequency of 6.8 per second.

After about one-half hour the subject appeared much more relaxed and less apprehensive about the experiment. The tremor continued as usual at 6.5 to 7.0 per second. Bursts of large amplitude rhythmic potentials, at the tremor frequency, now appeared in the brain potentials from all regions. Each burst lasted for about 3 seconds. They were more prominent from the frontal and central regions. Excitation of the subject at this time with an unexpected visual or auditory stimulation would produce again the excited brain potential picture with no large amplitude slow potentials. The tremor would continue undisturbed. It appears as if the continuous rhythmic subcortical discharges responsible for the tremor could momentarily control the synchronized beat of the cortical cells if the cortex was not sufficiently activated. The possibility of independent subcortical control of tremor which may momentarily take over control of cortical potential rhythms is demonstrated in this subject.

### *Paralysis agitans*

Two unilateral paralysis agitans patients were made available for study through the kindness of Dr. Westcott of Butler Hospital. These patients

showed no mental deterioration and had a slight tremor, within normal limits, on the right side. The digits of the left hand showed the continuous gross tremor of 4 to 5 per second, typical of patients with this disorder. Sample records of tremor movements from the index finger on the unaffected side taken together with brain potentials are shown in Fig. 3C. The brain potentials showed the typical normal alpha rhythm between 8 and 10 per second and a beta rhythm between 20 and 30 per second from either hemisphere.

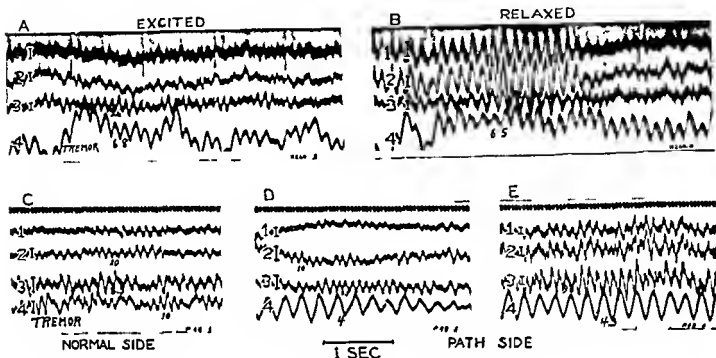


FIG 3 Brain Potentials and Abnormal Tremor. Records A-E brain potentials from frontal, precentral, and occipital head regions are shown in 1, 2, and 3 with finger tremor in 4. A and B are from subject H, T, excited with no correspondence between tremor and brain potentials and relaxed with large bursts of brain potentials at tremor frequency. C-E from unilateral paralysis agitans, patient W, showing correspondence between tremor and brain potentials on normal side (C) with no correspondence on affected side (D and E). Calibration lines equal 20 microvolts.

The tremor from this side also showed approximately the same combination of frequencies. The bipolar (D) and monopolar (E) records of brain potentials showed no relationship with the tremor from the affected side. That the tremor movements give a faithful picture of muscle activity was shown by the bursts of muscle potential from the flexor digitorum profundus preceding slightly each tremor movement.

In two other cases of more advanced bilateral paralysis agitans, short bursts of large amplitude brain potentials would occur occasionally at the tremor frequency in a manner similar to that described above for the "normal" subject F. T.

These cases demonstrate that the pathological process of paralysis agitans may be localized, in the unilateral cases, producing continuous rhythmic discharges which do not affect the tremor of the unaffected side nor do they appear to be related to cortical potential rhythms as is the normal tremor. In the more advanced cases the spontaneous rhythms of the cortex may be controlled, to a certain extent, by the more extensive subcortical discharges.

*Clonic movements and seizure waves in petit mal epilepsy*

Seizure waves, led off directly from the motor cortex in rabbits and monkeys during convulsions brought on experimentally by means of convulsant drugs or over-breathing, were shown by Kornmüller to have a fairly definite relationship to the frequency of clonic movements.<sup>20</sup> The relationship was not perfect and seizure waves could be detected at times when there was no evidence of any overt convulsion. Gibbs, Davis, and Lennox<sup>13</sup> had the impression that the frequency of clonic convulsive movements in epileptic patients was similar to that of the 3 per second discharges found from the cortical potentials as recorded through the skull. They report the presence of seizure waves in some patients without any detectable convulsive movements and also that seizure waves usually precede the convulsive movements at the beginning of an attack. Foerster and Altenburger<sup>11</sup> have obtained seizure waves directly from the motor cortex in man during brain surgery simultaneous with a Jacksonian attack of the right arm. Since muscle activity was not recorded with the seizure waves in these patients the precise relationship between the two phenomena is in need of further study.

Simultaneous records of brain potentials, clonic movements, and muscle potentials were obtained from three petit mal epileptic patients who usually showed minor motor manifestations at some time during the attack. Cortical potentials were taken from bipolar leads over the left precentral region. Clonic movements of the right index finger were recorded by the photo-cell method. Muscle potentials were obtained chiefly from silver wire electrodes on the skin surface over various arm and leg muscles. Concentric needle electrodes in the muscle did not prove satisfactory due to displacements of the base line with the muscle movements and to the difficulty of getting the needle over units which would be activated during the clonic contractions.

After the electrodes were placed, seizures were brought on by over-breathing. In all seizures, one to ten of the "spike" and slow wave patterns would appear before clonic movements could be detected. If the movements involved muscles from which the recording was made, each seizure wave might be accompanied by a burst of muscle potential after a latency of 50 to 60 milliseconds and by a clonic finger movement after a latency of about 100 milliseconds as shown in Fig. 4A and B. Little importance can now be attached to these latencies since it is often very difficult to determine from what part of the complex seizure wave they should be measured. They were measured from the beginning of the first "spike" which, in some cases, seemed to initiate the epileptiform discharge.

Simultaneous action potential records from the extensor digitorum and the gastrocnemius in one experiment gave apparent latencies of about 50 milliseconds to the gastrocnemius and about 100 milliseconds to the extensor digitorum (Fig. 4A). The aspect of the seizure wave from which this latency was measured to the gastrocnemius probably did not represent the same part of the cortical discharge for the extensor. This delay of about 50 milliseconds in the arrival of the impulse from the leg to the arm musculature may be

largely due to the conduction time from the leg to the arm area in the cortex since conduction velocity of such waves in the cortex has been shown by Adrian<sup>3</sup> to be from 5 to 50 or 60 cms. per second in anaesthetized animals.

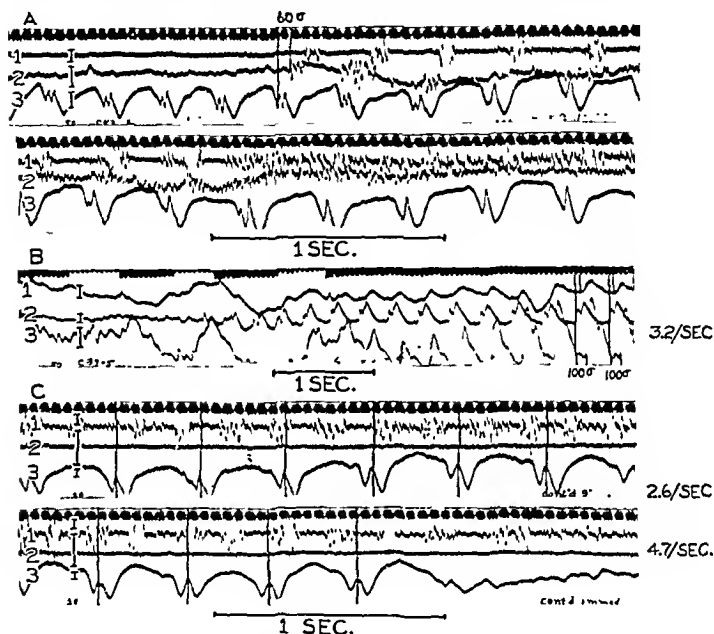


FIG. 4. Seizure Waves, Muscle Action Potentials, and Clonic Movements in Petit Mal Epilepsy. A. Patient H. T. during an attack. (1) Right digit extensor and (2) right gastrocnemius muscle potentials from surface electrodes. (3) Left precentral brain potentials. B. Same patient at beginning of another attack. (1) Potentials from needle electrode in right flexor of digits showing slow movement artifacts with muscle potentials scarcely visible. (2) Left precentral brain potentials. (3) Right index finger movements (photo-cell method). C. Same patient at end of another attack which did not involve the gastrocnemius. (1) Muscle potentials from right digit extensors and (2) right gastrocnemius (surface electrodes). (3) Left precentral brain potentials (bipolar leads). Calibration lines in A and B equal 50 microvolts, and in C equal 20 microvolts.

If one assumes that the conduction velocity may be 100 cms. per second in the unanaesthetized cortex this would imply a distance of about 5 cms. between the arm and leg areas which is not far from the right order of magnitude.

In the three patients used in this study, the convulsive movements

would play over the body musculature from one group of muscles to another throughout the attack in a manner which varied from one attack to another so that only in certain attacks could the above relationships between seizure waves and muscle activity be demonstrated. All attacks were accompanied by seizure waves but some attacks would miss completely certain muscle groups from which records were being taken. Also, occasionally, the bursts of muscle potential would occur at a frequency independent of the seizure waves as shown in Fig. 4C. In this example the seizure waves were at a frequency of about 2.6 per second, while the bursts of muscle potential were about 4.7 per second showing no relationship with the cortical discharges as recorded through the skull. This suggests the possibility that other nerve centers, which are apparently out of step with the cortical areas from which the potentials were obtained, may take over the control of the rhythmic muscle movements during the epileptic attack and that cortical potentials recorded through the skull from over the precentral region do not necessarily signalize excitatory processes reaching these final motor pathways.

#### DISCUSSION

It is difficult to arrive at definite conclusions from the above findings due to our lack of knowledge regarding the relationships between various efferent centers within the central grey matter which might affect impulses reaching the final common pathway especially with regard to spontaneous discharges in tremor or convulsive movements. The potentials recorded from bipolar leads on the scalp over a part of the cortex just anterior to the central fissure are almost certainly of cortical origin since potentials from deeplying regions could not be detected in this manner. However, the precise cortical origin of these potentials is not known. They may not arise, for the most part, from the motor region proper since it is largely buried within the central fissure. They may obtain their chief components from the premotor and frontal areas. In fact, electrodes farther forward on the head often give potential rhythms quite similar to those obtained from the region of the mid-sagittal point; both being different from occipital potentials.

Since Dusser de Barenne and McCulloch<sup>9</sup> have found a major spontaneous rhythm of 10 per second arises chiefly from the pyramidal cell layer of the motor cortex in the monkey, one might suppose that these slow potentials represent rhythmic depolarizations of cell surfaces which result in interrupted trains of impulses passing down the pyramidal tracts analogous to the mechanism found by Adrian and Buytendijk<sup>4</sup> in the respiratory centers of the goldfish. Heinbecker<sup>14</sup> has recently demonstrated a similar process in the isolated single heart ganglion cell of *Limulus*. It was surprising to find the beta rhythm of the cortical potentials also in the tremor movements. Jasper and Andrews<sup>19</sup> and Berger<sup>6</sup> have suggested that the beta rhythm may arise from different cortical cells than those producing the alpha rhythm but the mechanism by which these rhythms may also appear in the motor nerve discharges is not clear.

Dusser de Barenne<sup>8</sup> has shown a close functional relationship between spontaneous discharges from the sensory cortex in the monkey and the sensory projection areas in the thalamus. Local strychninization of either the thalamus or cortex would set the thalamo-cortical system "on fire." Gerard, Marshall, and Saul<sup>12</sup> report the same frequencies of spontaneous discharge throughout the visual system in the cat. It would appear from our findings on normal individuals that the spontaneous rhythmic activity of precentral regions of the cortex may be related to rhythmic discharges reaching the final motor pathways when the entire system is "at rest." Cortical activation through afferent channels may either control the tremor, causing an arrest of the slow rhythms in cortical potentials as well as in the tremor (the familiar arrest of paralysis agitans tremor with voluntary movement), or it may cause a dissociation of the cortical and subcortical motor centers, in this case usually causing an exaggerated tremor.

The continuous slow tremor unrelated to cortical discharges found in mild cases of paralysis agitans indicates that the controlling centers in this condition are subcortical; probably related to the striato-pallidal motor system. The breaking through of these subcortical discharges into the cortex when they become more extensive or with a decrease in cortical activation demonstrates the possibility of a close functional interrelationship between the spontaneous activity of cortical and subcortical motor systems. There is apparently a dynamic interplay between cortical and subcortical rhythmically discharging centers in competition, or, under normal resting conditions, integrated for the control of impulses reaching the final common path.

The occurrence of cortical seizure waves previous to the detection of motor disturbance in the epileptic patients shows that the excessive synchronized discharge in these cases first involves regions of the cortex not directly related to the motor system. As the seizure waves increased in magnitude the motor regions were involved, causing volleys of impulses to be set up in the motor nerves for each slow cortical potential. The lack of correspondence between the cortical seizure waves and bursts of muscle action potentials in some cases may be due to the setting up of autonomous discharging centers, probably subcortical, which may take over the control of certain motor pathways.

Kubie's<sup>22</sup> hypothesis in regard to the etiology of spontaneous movements is of particular interest in relation to the results of the present study. Continuous activity is assumed to be maintained in the "silent" areas of the brain by means of impulses conducted in closed circuits or reverberating, self-exciting, neuron chains. Since spontaneous activity, as indicated by rhythmic electrical activity at 10 per second, has been found to be almost continuously present also in the motor area of the monkey and related most specifically to the pyramidal cell layers, it is necessary to assume that continuous activity is not normally confined to Kubie's "silent" areas. The normal control of spontaneous movement appears to be due to the delicate integration of cortical and subcortical discharging centers rather than to the



blocking of discharges from "silent" areas to keep them from getting into the motor system. Spontaneous movements appear to a pathological degree when the synchronized discharge of large masses of cells becomes excessive, as in the epileptic attack; the smaller cell groups losing their individuality of differentiated function.

The continuity of rhythmic activity may not be dependent upon a self-exciting circuit of neurons but to the spontaneous repetitive firing of units which get into step through mutual facilitation as suggested by Adrian.<sup>1</sup> The nature of the spontaneous activity, although related to impulses arriving from other neurons, may be conditioned to a great extent by the chemical environment of the cells or the "blood stimulus" of Graham Brown,<sup>7</sup> thus determining not only the degree of spread of spontaneous activity as suggested by Kubie, but also being actually the "stimulus" for its maintenance since spontaneous firing of isolated axons may occur in certain rather definite chemical environments.<sup>10,23,24</sup>

#### SUMMARY

The relation between cortical potential rhythms as recorded through the unopened skull and tension rhythms in forearm musculature has been investigated by means of simultaneous records of finger tremors, muscle action potentials, and cortical potentials in normal subjects and in patients with paralysis agitans and petit mal epilepsy. The frequency of normal tremor movements was found to correspond closely with the frequency of potential rhythms from the regions of the cortex anterior to the central fissure; the major rhythm being at about 10 per second with a minor rhythm of about 25 per second. During normal sleep the tremor rhythms show changes which parallel the changes in cortical potential rhythm; namely, slow rhythms of about 5 per second and bursts of 13 to 14 per second waves.

Sensory stimulation may depress the tremor as it does the cortical potentials or may cause a dissociation between cortical potentials and tremor rhythms, the slow rhythms of the cortex being arrested simultaneously with an increase in amplitude of the tremor. It appears that there is an interrelationship between cortical and subcortical centers in the normal subject at rest which is reflected in the grouping of discharges which reach the final common pathway, but that this relationship may be disturbed by sensory stimulation. Also, the subcortical centers may dominate the tremor movements and become permanently dissociated from rhythmic cortical activity.

In exaggerated bilateral tremor in "normal" individuals there may be no relationship between cortical potential and tremor frequencies as long as the cortex is activated by sensory stimulation or conditions of general excitement or apprehension and the finger maintained in a given postural adjustment. With a decrease in cortical activation the cortical discharges may be periodically controlled by the subcortical activity and also, with a certain type of cortical activation as in voluntary contraction, the cortex may inhibit the subcortical discharges or take over the dominant control of the final common pathways.

The abnormal tremor of 4 to 5 per second in two unilateral paralysis agitans cases did not appear in the cortical potential rhythms which corresponded to the tremor of the unaffected side. In more advanced bilateral paralysis agitans cases the 4 to 5 per second rhythm would appear periodically in the cortical potential rhythms even though the tremor was continuous. It is concluded that the normal functional integration between cortical and subcortical motor centers is interrupted with only a moderate or unilateral involvement of the striato-pallidal motor system. More extensive bilateral involvement may produce subcortical activity which occasionally takes over the control of cortical rhythms.

Cortical seizure waves in epileptic patients may be associated with corresponding bursts of muscle potentials with clonic movements at 3 per second. The latency from the onset of the seizure wave to the muscle potential may be of the order of 50 milliseconds. The lack of correspondence between clonic movements and seizure waves in some attacks indicates that other centers, probably subcortical, may be set into autonomous activity and take over control of certain motor pathways

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## ACTIVATION OF HEAT LOSS MECHANISMS BY LOCAL HEATING OF THE BRAIN\*

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OF IMPORTANCE in the maintenance of a relatively constant body temperature are those heat loss activities which are brought into play on exposure to an excessively warm environment and aid in preventing the temperature of the body from becoming elevated above its normal range. In the cat, polypnea and panting are the most easily observed as well as the most important factors in the elimination of excessive bodily heat. Sweating is observed only on the pads of the feet, and peripheral vasodilatation is difficult to measure even with the most delicate thermocouples applied to the skin.

In the cat, panting usually does not occur in response to external heat until there is considerable rise of body temperature. An average rise of  $0.78^{\circ}\text{C}$ . occurred before panting began in a series of 43 cats subjected by Clark (1937) to external temperatures of  $40^{\circ}\text{C}$ ., but in five of these cats panting occurred before there was any rise in rectal temperature. The results in these five cats are suggestive of the reflex panting without rise in body temperature which is known to occur in the dog. Acknowledging the possibility that surface receptors may cause reflex panting in the cat, it is certain that the reaction is usually elicited by the elevation of body temperature.

A number of observations have indicated that an elevated intracranial temperature constitutes an effective stimulus for the activation of the heat loss mechanism. Warming the carotid blood entering the head has been shown (Kahn, 1904; Moorhouse, 1911; Hammouda, 1933) to cause sweating, peripheral vasodilatation, and hyperventilation in experimental animals, and the authors have inferred that these effects were produced by direct or central activation of regulating centers in the brain by the rising temperature of the blood.

Some support of this view has been provided by experiments in which parts of the brain have been heated directly, either by warm water passing through a closed tube inserted in or applied to the desired region, or by open irrigation with warm saline. Barbour (1912), Hashimoto (1915) and Prince and Hahn (1918) found a fall in body temperature resulted from heating the corpus striatum in the rabbit and cat, and the first two workers described a peripheral vasodilatation during this procedure. Moore (1918) confirmed the antipyretic action of warming this region but showed that the corpus striatum was not specifically related to the effect, and Sachs and Green (1917) could not observe any constant result of warming or irritating the corpus striatum in various other ways. It has been pointed out by Bazett (1927)

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that the effects obtained by Barbour and others were probably produced at some distance from the site of heating in the corpus striatum because of the high temperatures which had to be used to obtain reactions. Hasama (1929) found a fall in body temperature to result from warming the base of the hypothalamus and preoptic region in the cat, and observed a profuse sweating on the footpads during this procedure. Irrigation of the third ventricle with warm saline was shown to produce polypnea and panting in the dog by Hammouda (1933). These observations are not altogether consistent but appear to indicate that a rising intracranial temperature is able to activate the heat loss mechanism.

In the course of a series of investigations in this laboratory of the rôle of the hypothalamus in the central regulation of body temperature (Ranson and Ingram, 1935; Teague and Ranson, 1936; Ranson, Fisher and Ingram, 1937; Ranson, Jr., 1938) it became desirable to reinvestigate the central action of heat in initiating heat loss activities and to attempt a more precise localization of the portion of the brain concerned.

#### METHODS

As a first step in this direction an apparatus was assembled which provided a high frequency alternating current, whose warming effect could be altered as desired by changing the voltage. The low power high-frequency unit consisted of a rectifier with an output of 600 volts at 50 ma., and a tuned-plate tuned-grid oscillator. A type 10 tube was used for the oscillator and its plate and grid tank circuits were calculated to oscillate at 1,000,000 cycles. The voltage across the electrodes was measured with a cathode ray oscillograph. It was convenient to measure voltages from peak to peak on the face of the tube and then divide by 2.8 to obtain the r.m.s. (root mean square) alternating current. Cats were used and the desired region of the brain was heated by passing the current between 2 electrodes or occasionally between 2 pairs of electrodes oriented within the brain with the aid of the Horsley-Clarke stereotaxic instrument. The electrodes, which consisted of straight lengths of 22 gauge nichrome wire, insulated with enamel to within 2 mm. of the exposed pointed tip, were fixed in a multiple needle carrier and inserted vertically through the dura after reflection of the skin and temporal muscles and removal of the appropriate portion of the calvarium. The location of the electrodes and the amount of damage done to the brain was checked in most of the experiments by the microscopical study of serial sections of the brains. Urethane in a dosage of 1 gm. per kilo, intraperitoneally, was the anesthetic employed and a consideration of the use of anesthetics in these experiments is presented elsewhere (Magoun, 1938). Whenever the initial polypneic panting which occurred in about one-third of the cases under urethane was present, ample time or fall in body temperature was allowed for its disappearance. We have considered the subsequent reactions to heating the brain in these animals valid, for the specificity of the nature and location of this stimulus was repeatedly demonstrated and extensively controlled by equally good or better results from other animals in which no such anesthetic effects were apparent.

In control experiments an iron-nichrome thermocouple, oriented in the posterior electrode carrier of the Horsley-Clarke instrument, was used to measure the temperature rise of the tissues around the electrodes during heating. The thermocouple tip was enameled in an attempt to prevent electrostatic pickup but Huxton (1937) thinks this results in too high a reading. During our calibration of the apparatus with 11 and with 14.3 volts (r.m.s.) across the electrodes, it was found that 1 mm. laterally from the nearest electrode, the rises in brain temperature were 2.1° and 3.7°C. respectively and at 2 mm. laterally 0.7° and 1.2°C. Under the same conditions a thermocouple between the electrodes and 1 mm. from the nearest was raised 3.7° and 6.3°C. according to the voltage employed. These values indicate an increase in temperature of 75 per cent at 14.3 volts over that produced at 11 volts. After the current was turned on it took about one minute or more for the tissue to reach its highest temperature. At that time the rate of cooling

by the blood and conduction by the tissues equalled the rate of heat production. After current was turned off the tissue cooled rapidly at first and then more slowly to reach normal in about 2.5 to 3.5 minutes.

Since the rectal temperatures of the animals averaged  $36.6^{\circ}\text{C}.$ , an increase of  $3.7^{\circ}\text{C}.$  caused by 11 volts would bring the region 1 mm. from the electrode to a temperature of about  $40.5^{\circ}$ , which is not destructively high. An increase of  $6.3^{\circ}$  caused by 14.3 volts (r.m.s.) would bring the temperature at 1 mm. from the electrode to about  $43.0^{\circ}$  which would account for the damage done to the brain tissue in some of these experiments. These calculations are based on the assumption that the temperature of the brain is normally about the same as that of the rectum. A study of our data in the light of the observation reported by Huntoon (1937) would indicate that our thermocouple readings were too high rather than too low.

## RESULTS

In a large series of experiments extensive exploration of the forebrain and midbrain of the cat revealed only a limited region of the brain from which responses to heating could be obtained. Local heating of this reactive area caused a marked acceleration of respiration, the excursion of which became very shallow. At a variable time after the increase in respiration began, the mouth was opened and rhythmic movements of the nostrils, angles of the mouth, and tongue appeared with each respiratory excursion. When at their peak these respiratory alterations constituted a characteristic "polypneic panting," and were frequently, but not invariably, accompanied by the appearance of sweat on the foot pads. The responses were in all points similar to those obtained by heating the entire animal.

The region of the brain from which these reactions were elicited on heating is schematically indicated on a paramedian sagittal section through the brain of the cat, shown in Fig. 1. The rostral portion of the reactive area is seen to be located in the ventrocaudal part of the telencephalon, between the anterior commissure dorsally and the optic chiasma ventrally. Its anterior limits extend a little farther forward than the preoptic area and the crossing of the anterior commissure. The responsive region is continued backward through the diencephalon in the dorsal part of the hypothalamus and the ventral part of the thalamus and at more caudal levels occupies a progressively more dorsal location. At the transition to the midbrain it is located in the vicinity of the central grey matter surrounding the anterior end of the cerebral aqueduct.

The rostral portion of the reactive region, which is cross-lined in Fig. 1. and which includes the preoptic area and the suprachiasmatic portion of the hypothalamus, has yielded better responses than the more caudal portion extending backward through the diencephalon. Heating this rostral region induced acceleration of respiration to an average rate of 255 excursions per minute. Panting appeared spontaneously and was marked and continuous throughout the responses. In many instances these pronounced respiratory alterations during heating were accompanied by the appearance of sweat on the foot pads.

In several respects the responses to heating the reactive region through the diencephalon, enclosed in dotted lines in Fig. 1. were weaker than those

just considered. The responses from the diencephalon were less abrupt in onset, required a longer time to reach their peak and were quantitatively smaller, the average polypnea amounting only to 155 excursions per minute. In addition, the panting associated with the responses from the diencephalon only persisted for brief periods and usually required the facilitation provided by holding the mouth open (Lilienthal and Otenasek, 1937) to appear at all.

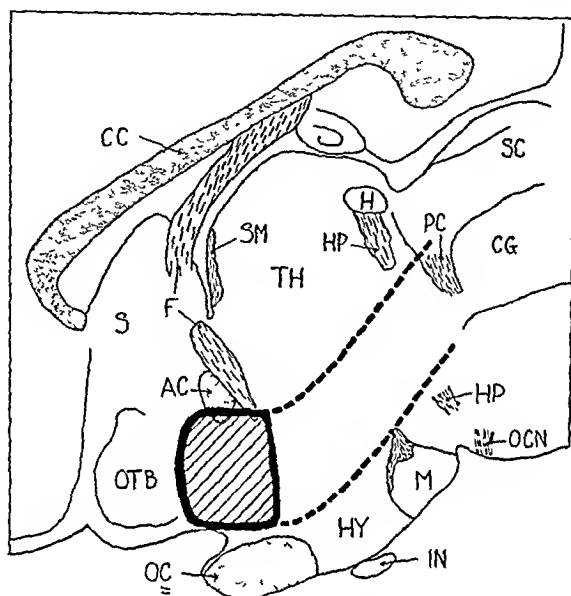


FIG. 1. Schematic outline of the region reactive to heating, projected on a paramedian sagittal section through the brain of the cat. Abbreviations for all figures are as follows:

AC	anterior commissure	HY	hypothalamus	OCN	oculomotor nerve
BP	basis pedunculi	IC	internal capsule	OT	optic tract
C	caudate nucleus	IN	infundibulum	OTB	olfactory tubercle
CC	corpus callosum	LV	lateral ventricle	PC	posterior commissure
CG	central grey matter	M	mammillary body	S	septum
E	entopeduncular nucleus	MB	midbrain	SC	superior colliculus
F	fornix	MFB	medial forebrain bundle	SM	stria medullaris
GP	globus pallidus	MT	mammillo-thalamic tract	TH	thalamus
H	habenula	OC	optic chiasma	3V	third ventricle
HP	habenulo-peduncular tract				

The difference in reactivity, in our opinion, indicates a reduced concentration of reactive elements in the responsive field through the diencephalon.

It has been mentioned that the reactive region shown in Fig. 1 is the only portion of the brain studied which responds to local heating and this statement is based upon the negative results obtained to heating at locations distributed through a large portion of the cerebral cortex, the subcortical white matter, the ventral telencephalon rostral to the reactive area, the

caudate and lentiform nuclei of the corpus striatum, the diencephalon surrounding the responsive field and the midbrain behind it as far caudad as the anterior end of the pons. The absence of response from these negative regions was checked by heating at varying positions out to 8 mm. lateral from the midline and at varying dorsoventral locations extending from the dorsal surface of the cerebral hemispheres to the base of the brain. In such exploration the negative results elsewhere were validated by characteristic responses obtained from the reactive region shown in Fig. 1 at the beginning and end of the experiments.

With this introduction, a series of representative protocols may be presented in which the region between and around two electrodes inserted 2 mm. to either side of the midline was heated at succeeding dorsoventral locations in 6 transverse planes extending in serial order from a level just in front of the anterior commissure through the diencephalon to the anterior end of the midbrain, i.e., through the area of distribution of the reactive field shown in Fig. 1. The location of the electrodes and the respiratory responses to heating in each of these protocols are illustrated in Figs. 2-7.

#### PROTOCOLS

*Protocol 1 (Cat 1, Fig 2)* The first protocol illustrates the responses to heating at a level  $\frac{1}{2}$  mm rostral to the crossing of the anterior commissure and extending ventrally through the anterior tip of the optic chiasma. Positions a, b, c, d in Fig 2A show the location of the electrodes during each period of heating and the respective reactions obtained are charted in Fig 2B. The absence of response to heating at location a, obviously indicates that this region was negative and such negative locations need not be commented

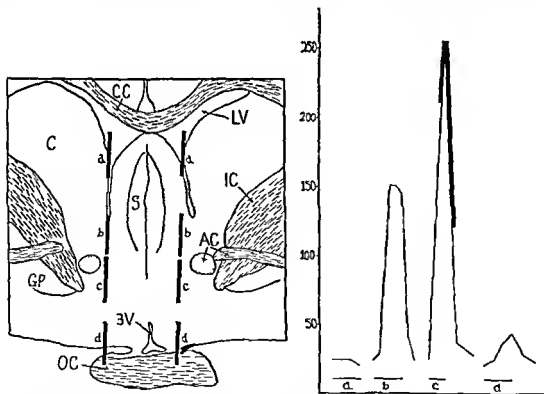


FIG 2A Transverse section through the brain of Cat 1. The positions of the two electrodes during heating are shown at a, b, c, and d.

FIG 2B Chart showing the respective respiratory responses obtained from heating at positions a, b, c and d, Fig 2A. The rate of respiration is shown on the ordinate, panting is shown by a heavy line. Period a represents 5 min, other times are in proportion.



upon further. It can be seen that heating at position c, Fig. 2A, at a vertical level corresponding to that of the anterior commissure and the region ventral to it, induced (response c, Fig. 2B) an increase in respiratory rate from 25 to 252/min. with panting (heavy line in chart). A considerably weaker response (b, Fig. 2B) was obtained on heating at position b, dorsal to the location of the anterior commissure and wherever in these experiments a weak reaction was obtained from a location immediately above or below that yielding a good response, we have been inclined to consider the possibility of spread of heat to the closely adjacent more reactive region. It should be noted that heating at position d, where the meninges at the base of the brain were undoubtedly warmed was almost negative (d, Fig. 2B), and the responsive region is clearly seen to lie within the brain. This has been repeatedly verified in many experiments.

*Protocol 2 (Cat 2, Fig. 3).* The second protocol illustrates the response to heating at the level of the crossing of the anterior commissure. The location of the electrodes is shown in Fig. 3A, and the responses to heating are charted in Fig. 3B. Heating at location d, for

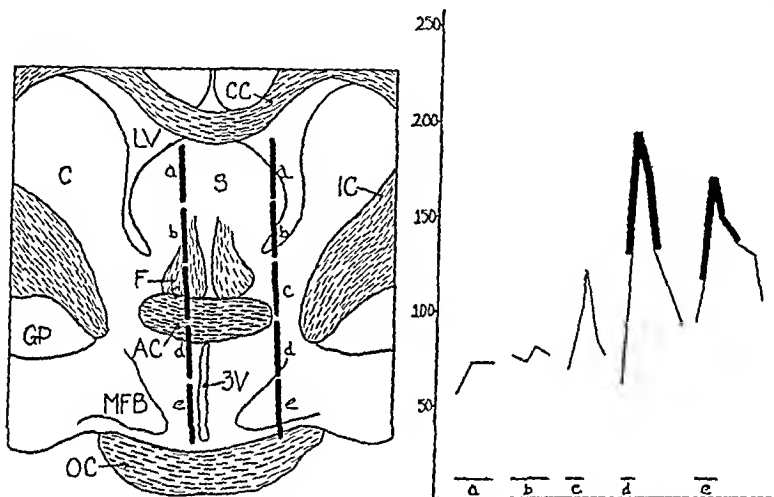


FIG. 3A. Transverse section through brain of Cat 2. The positions of the two electrodes during heating are shown at a, b, c, d and e.

FIG. 3B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c, d and e, Fig. 3A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period a represents 5 min., other times are in proportion.

the most part ventral to the anterior commissure, produced (response d, Fig. 3B) an increase in respiration from 60 to 192/min. with panting. Heating at location c immediately dorsal to that just described, yielded a much weaker response (c, Fig. 3B), and at location e, immediately ventral to it a slightly weaker reaction with increase of respiration to 168/min. and panting (e, Fig. 3B). The best response (d, Fig. 3B) was somewhat weaker than those usually obtained from this region which may have been due either to the brief period of heating or to the asymmetrical position of the electrodes with reference to the midline (Fig. 3A).

*Protocol 3 (Cat 3, Fig. 4).* The third protocol illustrates a response to heating the suprachiasmatic hypothalamus at a level  $\frac{1}{2}$  mm. caudal to the crossing of the anterior commissure. The position of the electrodes is shown in Fig. 4A and heating produced an increase in respiratory rate from 36 to 288/min. with panting (Fig. 4B). Unfortunately other dorsoventral locations were not heated in this animal but the marked response obtained from this position indicates that it lies at or very close to the responsive center.

*Protocol 4 (Cat 4, Fig. 5).* The fourth protocol illustrates the responses obtained at a level through the anterior thalamic nuclei above and through the infundibulum below.



FIG 4A Transverse section through the brain of Cat 3 The position of the two electrodes during heating is shown at a

FIG 4B Chart showing the respiratory response obtained from heating at position a, Fig 4A The rate of respiration is indicated on the ordinate, panting is shown by a heavy line Period a represents  $2\frac{1}{2}$  min

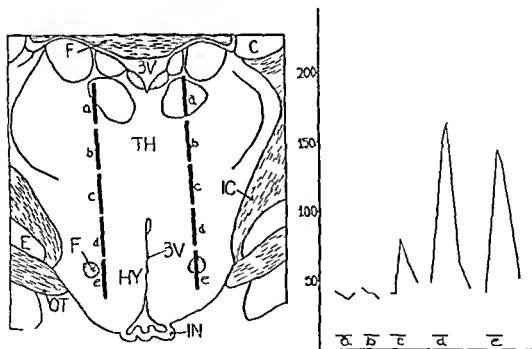


FIG 5A Transverse section through the brain of Cat 4 The positions of the two electrodes during heating are shown at a, b, c, d and e

FIG 5B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c, d and e, Fig 5A The rate of respiration is indicated on the ordinate Period a represents 3 min, other times are in proportion

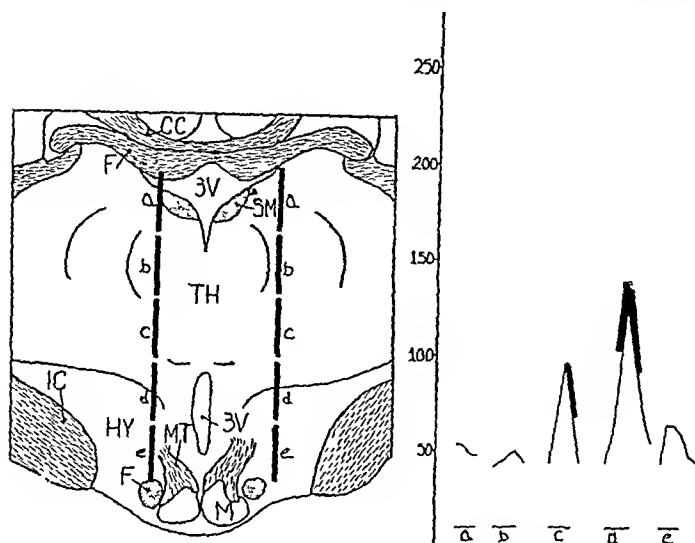


FIG. 6A. Transverse section through brain of Cat 5. The positions of the two electrodes during heating are shown at a, b, c, d and e.

FIG. 6B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c, d and e, Fig. 6A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period a represents 3 min.; other times are in proportion.

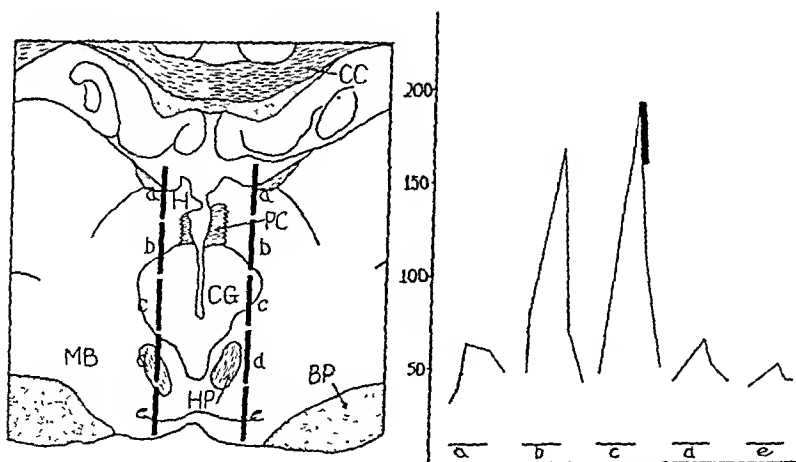


FIG. 7A. Transverse section through the brain of Cat. 6. The position of the electrodes during heating is shown at a, b, c, d, and e.

FIG. 7B. Chart showing the respective respiratory responses obtained from heating at positions a, b, c, d and e, Fig. 7A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period a represents 5 min.; other times are in proportion.

Heating at location d produced an increase in respiratory rate from 48 to 164/min<sup>1</sup> without panting (d, Fig 5B). Heating at location e produced an increase in the rate of respiration from 40 to 144/min (e, Fig 5B) and though there was no spontaneous panting the animal panted for a brief period when the mouth was held open.

*Protocol 5 (Cat 5, Fig 6).* The fifth protocol illustrates the reactions to heating at a level through the nucleus medialis dorsalis of the thalamus above and through the mammillary bodies below. Heating at location c produced an increase in respiratory rate from 44 to 96/min with panting (c, Fig 6B). Heating at location d produced an increase in the rate of respiration from 44 to 138/min with panting (d, Fig 6B). Heating at location e produced a slight increase in respiration from 44 to 64/min.

*Protocol 6 (Cat 6, Fig 7)* The sixth protocol illustrates the responses to heating at a level through the caudal tip of the habenulae and the rostral fibers of the posterior commissure above, and through the rostral portion of the midbrain  $\frac{1}{2}$  mm behind the mammillary bodies, below. The best response was obtained from location c where heating produced an increase in respiratory rate from 48 to 192/min with a short period of slight spontaneous panting (c, Fig 7B). Stronger heating at location b immediately dorsal to that just considered gave a slightly weaker response, the respiratory rate increasing to 168/min (b, Fig 7B). The responses to heating this transition region from diencephalon to midbrain were somewhat more marked than those elicited from more rostral regions of the diencephalon in other animals. This may be accounted for either on the basis of the variation present in different experiments or by the supposition of a concentration of reactive elements in the transition region from diencephalon to mid-brain comparable to that more evidently present in the ventral part of the telencephalon.

The results which have just been described have been presented first to provide an initial survey of the nature of the reactions and the location of the responsive region to heating the brain. Additional information on several points may now be presented.

*Lateral limits of responsive area.* The responses obtained to heating between and around electrodes situated 2 mm. to either side of the midline in the experiments just described and many others imply a medial location of the reactive region and this is supported by the results from an experiment in which two electrodes were inserted almost in the midline, one in the pre-optic region and the other behind it in the anterior hypothalamus. Heating the midline region between the electrodes induced an increase in respiratory rate from 48 to 240/min. with panting, i.e., a marked response.

A large amount of negative data was accumulated to heating between electrodes situated 4 and 8 mm. lateral to the midline, and it is safe to conclude that the responsive elements are concentrated within 4 mm. of either side of the midsagittal plane. There are many indications that the lateral limits of this concentration may be still more medially placed. The schematic outline of the reactive field shown in Fig. 1 is projected on a sagittal plane 1 mm. lateral to the midline, but only to indicate in a general way its medial location.

*Time relations of responses* In a large number of marked reactions from the ventral telencephalon, the acceleration of respiratory rate began between  $\frac{1}{2}$  and  $1\frac{1}{2}$  min. after the onset of heating. Since 1 min. or more was required after the onset of heating for the tissues to reach their highest temperature (see Methods), the actual latent period of the reaction was probably very brief. Once begun the increase in respiratory rate was fairly abrupt and the peak rate was reached between 1 and 4 min., usually between 2 and 3 min.

after the onset of heating. Panting began 1 to 2½ min. after the onset of heating, at respiratory rates ranging between 80 and 210/min. When sweating was present it was usually observed between 1½ and 2 min. after the onset of heating.

When heating was discontinued the respiratory rate fell at first abruptly and then more slowly until the original basal rate or one slightly higher was reached after 1½ to 6 min., usually after 2 to 4 min. Panting stopped between ½ and 2 min. after the cessation of heating at respiratory rates ranging from 120 to 150/min. The time required for deceleration of respiration and cessation of panting after heating was discontinued, corresponded closely to that required for the tissues to cool (see Methods).

*Repetition of heating.* In each of several animals the rostral portion of the reactive region was repeatedly heated between two pairs of electrodes with results confirmatory of those already presented. The results from one experiment (Cat 7) are illustrated in Fig. 8. One pair of electrodes was inserted in a plane through the crossing of the anterior commissure and another pair in a plane through the infundibulum (Fig. 8A). The preoptic region and anterior hypothalamus enclosed between the electrodes was repeatedly heated with the results shown in Fig. 8B.

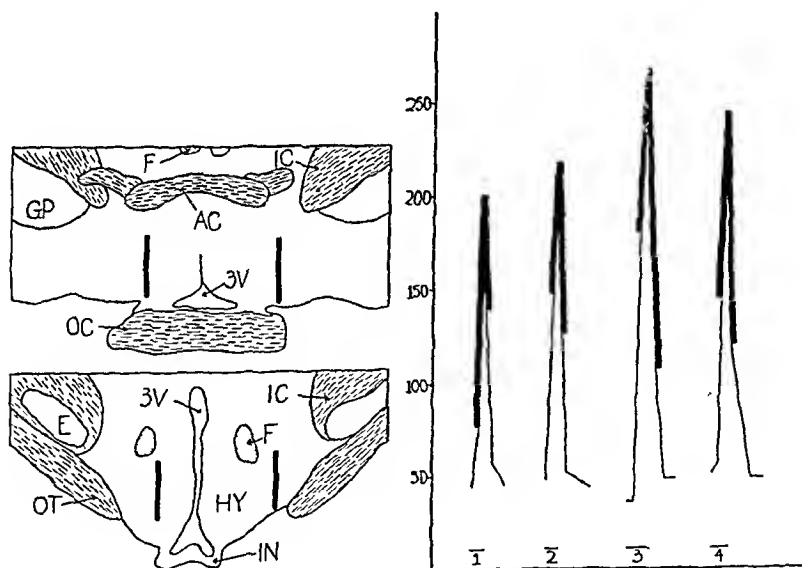


FIG. 8A. Two transverse sections through the brain of Cat. 7. The position of the rostral pair of electrodes during heating is shown in the upper section, that of the caudal pair is shown in the lower section.

FIG. 8B. Chart showing the respiratory responses obtained to repeated heating of the region between the electrodes shown in Fig. 8A. The rate of respiration is indicated on the ordinate; panting is shown by a heavy line. Period 1 represents 1½ min.; other times are in proportion.

Initial heating for  $1\frac{1}{2}$  min. induced an increase in respiratory rate from 44 to 198/min. with panting (response 1, Fig. 8B). After a 15 min. interval a second period of heating for  $1\frac{1}{2}$  min. induced an increase in the rate of respiration from 48 to 216/min. with panting and the appearance of sweat on the footpads (response 2, Fig. 8B). Following another 15 min. interval, a third period of heating for 3 min. induced an increase in respiratory rate from 36 to 264/min. with panting and the appearance of sweat on the footpads (response 3, Fig. 8B). Following a 20 min. interval, a fourth period of heating for 2 min. induced an increase in the rate of respiration from 48 to 240/min. with panting (response 4, Fig. 8B). Information on repetition of responses was usually gained in experiments in which the region of the brain between two pairs of electrodes was heated because such experiments were not appropriate for the study of detailed localization. The responses to heating the region of the brain between a single pair of electrodes could be repeated just as satisfactorily, however.

*Distinction between effects of faradic stimulation and heating.* In the intervals between heating in the experiment just described and in several others, the effect of faradic stimulation of the region of the brain between the electrodes was observed. This regularly led to sympathetic discharge, due to excitation of hypothalamus, causing maximal dilatation of the pupils, maximal retraction of the nictitating membranes, erection of the hair on the back and sometimes occasioned struggling. Respiration was accelerated, sometimes after an initial apnea, respiratory excursions were deep and labored and occasionally were associated with facio-vocal activity as in other experiments (Kabat, 1936; Magoun, Atlas, Ingersoll and Ranson, 1937). In one instance faradic stimulation produced panting and we have occasionally observed panting in response to faradic stimulation of the anterior hypothalamus in other experiments.

In contrast to this indiscriminate action of faradic stimulation which excited everything within range, the effect of heating was specific and precise, leading only to the excitation of heat loss mechanisms. During the responses to heating, the pupils and nictitating membranes remained unchanged and there was no erection of hair or struggling.

*Body temperature.* The rectal temperature at which a group of 25 marked responses to heating the ventral telencephalon were obtained in these experiments ranged from 35.0 to 38.4°C. The larger number (19) of these responses was elicited at rectal temperatures between 35.5 and 37.5°C., which are subnormal and demonstrate that an elevated body temperature is not essential for the initiation of heat loss activity when the appropriate region of the brain is adequately heated.

Heat loss activities were not maintained for a long enough time in any of these experiments to produce a clearcut depression in body temperature beyond the gradual fall which took place in each instance as a result of the anesthesia.

*Effect on the brain.* A histological study was made of the brains of most of the animals used in this investigation and permitted the determination of any damage done to the brain by heating. A voltage of 11 was employed in heating the responsive region in the ventral telencephalon in a total of 9 instances with no damage to the brain. In heating this region, 14.3 volts were employed in 11 instances without damage or with only very slight damage in the immediate vicinity of the electrodes. In 9 other instances heating the ventral telencephalon with 14.3 volts resulted in moderate to marked damage of the brain around and between the electrodes.

A voltage of 11 was employed in heating the responsive region in the diencephalon in one instance with no damage to the brain. In heating this region 14.3 volts were used in three instances with slight damage to the brain in the immediate vicinity of the electrodes. In five instances heating the diencephalon with 14.3 volts caused moderate to marked damage of the brain around and between the electrodes. In both the telencephalon and diencephalon the usual responses were obtained in the instances when the brain was damaged and presumably were elicited from the adjacent reactive region outside the area of damage.

In a number of preliminary experiments in this series excessive heating (28.6 volts) of the area rostral or dorsal to the reactive region shown in Fig. 1 produced the usual responses. These responses could not have been obtained from the area in the vicinity of the electrodes, however, for in such instances this area was widely destroyed by the excessive heat employed. In our opinion, such reactions were obtained from spread of heat to the responsive region shown in Fig. 1. In all instances when damage occurred the responses subsided just as rapidly following cessation of heating as when no damage was present. The experiments in which the brain was damaged provide little evidence for localization and throughout this presentation the emphasis has been placed on those results which were obtained with a minimum amount of heating and with little or no injury to the brain.

## DISCUSSION

It may be noted that the region in the ventral telencephalon responsive to heating, overlaps to some extent the ventral and caudal distribution of what is probably a descending cortical pathway for respiratory inhibition, yielding a decrease in respiratory rate and amplitude when activated by localized faradic stimulation (Kabat, 1936). The appearance of polypneic panting in acutely decorticate animals has recently been attributed by Lilienthal and Otenasek (1937) to release from cortical inhibition through destruction of such a pathway. Lest the same explanation suggest itself for the responses to local heating of the reactive region delimited in these experiments, it may be emphasized that these responses to heating were not dependent upon such destruction, for the larger number of reactions were obtained without appreciable injury to the brain. Furthermore, had these responses been dependent upon destruction, they should have continued

indefinitely instead of disappearing as they did with the cessation of heating. Repetition of the responses should have been impossible, yet they could be repeated apparently indefinitely.

To us the obvious interpretation of these results is that in these experiments we have been setting into play by artificial heating the same mechanisms in the same regions of the brain which are activated in the normal animal when the temperature of the blood rises above normal. Such an interpretation provides a logical explanation of the results obtained in a study of the effect of lesions in this region which, as has been shown by Teague and Ranson (1936) and by Clark, Magoun and Ranson (in preparation), abolish the animal's ability to regulate effectively against high environmental temperatures. Further consideration of the results of these experiments from the point of view of the central regulation of body temperature will be presented elsewhere (Clark, Magoun and Ranson, in preparation).

The results of these experiments should not be taken to indicate that the region responsive to heating contains the final efferent collection of supranuclear neurons for coordinated polypneic panting, for this may still be obtained after the area here delimited has been largely (Lilienthal and Otenasek, 1937) or entirely (Keller, 1933) destroyed. The responsive area to heating found in these experiments may contain afferent-like elements capable of exciting efferent groups of neurons situated at more caudal levels.

#### SUMMARY

Local heating of the brain of the cat with low voltage, high frequency current passing between electrodes oriented with the Horsley-Clarke apparatus has demonstrated a reactive region which responds to heating by marked acceleration of respiratory rate, panting and in some instances by the appearance of sweat on the foot pads.

The reactive elements appear to be concentrated in the medial portion of the caudal part of the ventral telencephalon and, in lesser concentration, are continued backward through the diencephalon as far as the anterior end of the midbrain. In the telencephalon the responsive region occupies a position between the anterior commissure and the base of the brain. Through the diencephalon it is located in the dorsal part of the hypothalamus and the ventral part of the thalamus, and occupies a progressively more dorsal position at more caudal levels. At the anterior end of the midbrain it is located in the vicinity of the central gray matter surrounding the transition from third ventricle to cerebral aqueduct.

The results are interpreted as indicating that the reactive region contains structures which are activated by the rising temperature of the blood and lead to heat loss activity in the normal animal when overheated.

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# LOCALIZED THERMAL CHANGES IN THE CAT'S BRAIN\*

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THE Horsley-Clark instrument has been used in this laboratory for the study of local electrical (Gerard, Marshall and Saul, 1936) and metabolic (Brookens, Ectors and Gerard, 1936) activity in known anatomical structures in the brain. It seemed probable that temperature could be successfully studied with the same apparatus carrying a thermojunction, and information thus be obtained on the energy liberation of active nerve cells, the vasomotor concomitants of activity, or both.

Heat production of the isolated frog spinal cord, under direct or reflex activation, has been studied by several workers, and the most complete evidence (Holzlöhner and Trurnit, 1937) indicates a reasonable parallelism to peripheral nerve. A total heat up to  $10^{-3}$  cal./gm. is liberated during 5 to 12 minutes ( $18^{\circ}\text{C}.$ ) following one second of stimulation with 80 induction shocks per second applied at the end of the cord away from the thermopile. Of this, about 3 per cent is initial heat, and the remainder recovery heat plus any due to repetitive discharges. This active heat production is about twice the resting heat rate,  $5 \times 10^{-4}$  cal./gm./sec., as estimated from respiration data (Rosenberg, 1935; Batz, 1923). For the frog sciatic, equivalent values are  $8 \times 10^{-6}$  cal. initial heat,  $5 \times 10^{-6}$  cal. total—duration 30 minutes, at  $20^{\circ}\text{C}.$ —per second of stimulation at maximal activity (see Feng, 1936). Per single impulse, the initial heat is  $7 \times 10^{-8}$  cal. gm., total  $2 \times 10^{-6}$ . In the non-medullated leg nerve of the spider crab at maximal stimulation, initial heat per gm./sec. is about 10 times that of frog nerve under similar conditions, and total heat is 18 or more times as great. In terms of maximal evoked activity, then, the total heat produced by the frog spinal cord is well over 20 times that of the sciatic nerve. If comparisons are made at lower frequencies of stimulation (e.g., 8/sec.) the ratio is much higher, up to 100 times—possibly because of repetitive discharges by the central units.

Two other factors must, however, be considered, both of which would tend to multiply the true difference between cells and fibers. 1. In nerve, a maximal stimulus activates all the units; while stimulation of the lumbar cord—presumably of ascending motor paths—engages only a fraction of the neurons and may inhibit the activity of many. 2. In nerve, the neural elements compose one to two-thirds of the total mass; in brain, possibly as little as 1 per cent. The energy per unit of mass per single activation may, therefore, be several hundred times as great in a nerve cell as in its axon.

On turning to the mammalian brain *in situ*, a further temperature difference appears, as well as the complication of a circulation. No work to date measures the true heat production of activity, and even the increased oxygen

\* A preliminary report of this work appeared in the *Amer. J. Physiol.*, 1936, 115: 59.

consumption of active brain is highly uncertain. Resting respiration rates are rather more dependable—some 5000 cmm./gm./hr. for cat cortex at the moment of removal (Brookens, Ectors, and Gerard, 1936 and unpublished; Schmidt, 1928), against 180 for dog nerve, also at 37°C.—and if the increase on activity is proportional, brain heat is about 30 times that of nerve, per equal gross mass; or  $1.5 \times 10^{-3}$  to  $4.5 \times 10^{-3}$  cal./gm./sec. (depending on whether a 100 or 300 per cent increase is assumed for activity). One might anticipate, then, a heat production of the order of  $6 \times 10^{-5}$  cal. per impulse in an active portion of the brain; and if the rather arbitrary figure of 50 discharges per second be assumed for activity evoked by sensory stimulation (at least electrical discharges well over this frequency do occur) brain temperature would ultimately rise at the rate of 0.003°C./sec., aside from heat loss. This same value for maximal active heat production is obtained by doubling the resting level; a relation seen to hold also for frog cord and, except under special conditions, for frog nerve.

Heat loss, however, is continuous; partly by conduction and radiation through the skull or from the exposed brain surface, mainly through the blood stream. The actual temperature change in a region of the brain, associated with its activity, will be a balance between the extra heat produced—depending on degree of excitation, concentration of active cells, absolute heat production, duration of total heat, etc.—and the extra heat lost—depending on blood-brain temperature difference, richness of vascular bed, volume of blood passing, etc. Blood flow is, of course, the important variable; and a vasodilatation accompanying activity might well overshadow an increased heat production so that brain temperature is actually lowered.

To some extent it has been possible to disentangle these several factors, as will be discussed, but fortunately the cause of thermal changes is irrelevant to one important aspect of our study—evidence of local alterations in individual sensory systems when these are stimulated via appropriate receptors.

Renewed extensive studies of the control of brain circulation (see Wolff, 1936, for recent summary) have utilized, among others, thermal methods for measuring flow. In Gibbs' (1933) arrangement, the thermojunctions are continually warmed above blood temperature and an increased blood flow has a consequent cooling effect; in Schmidt and Pierson's (1934) the junctions are cooled and increased flow warms them. Steep temperature gradients are maintained, with several degrees difference between needle and blood, so that any true neural heat production would not be seen. In the recent work of Feitelberg and Lampl (1935), however, using one thermojunction in the brain and the other in the carotid artery, the small temperature difference may well include true neuron heat; and in many respects our results are in agreement with theirs.

#### METHODS

A thermoneedle, 20 gauge hypodermic needle with a single junction of 38 gauge constantan and enamelled copper wires insulated with bakelite varnish, was arranged to fit on a brass rod clamped in the carriage of the Horsley-Clark instrument. The wires, in separate rubber tubing, ran 75 cm. to the constant temperature junction, embedded in

a brass block and kept in an ice and water mixture. For certain experiments the second junction, also in a needle, was inserted in a blood vessel or the abdomen. The entire circuit, including a potential divider, series and shunt resistances, and a Moll Z'd galvanometer, was of copper with fixed connections. A variable and reversible balancing potential was thrown into the fixed divider in the usual manner.

The resistance of the thermal elements, 43 ohms, was about that of the galvanometer, 30 ohms. The sensitivity, by calculation and by direct calibration, was 1 mm deflection (scale at 1.25 m) = 0.00075°C (in some experiments 1 mm = 0.001°C). With additional series and shunt resistances in, a less sensitive combination, 1 mm = 0.003°C, was used for preliminary orientation or to follow larger temperature changes. Movements of the galvanometer spot were followed manually with a rack and pinion stylus activating a writing point on a kymograph, and continuous records obtained.

Experiments were performed on 35 cats and 3 dogs under nembutal (35 mgms./kilo, intraperitoneally) or basal nembutal (25 mgm./kilo) supplemented with ether. The Horley-Clark instrument was attached as usual and set at the desired A-P and R-L coordinates. A small skin incision was made at the indicated position and the skull drilled (1 mm hole) to admit the needle. Before or after placing the thermojunction, a concentric electrode was usually inserted to the same depth and action potentials in response to optic or somesthetic stimulation observed, thus insuring that temperature observations were made in the desired sensory pathway. A light shining into the eyes for  $\frac{1}{2}$  to 2 minutes, squeezing and manipulating the toes of the contralateral forepaw over similar periods, and ammonia vapor blown into the nostrils constituted the stimuli used.

## RESULTS

*Anaesthetic effect.* Brain temperature falls rapidly under the influence of an anaesthetic or narcotic drug. The amount of fall can be estimated only from animals with indwelling thermocouples, since in acute experiments a change has already occurred when observations begin. Even so, after intraperitoneal nembutal and the 30 to 40 minutes required to place the instrument, the brain cools a further 1.2 to 1.5° during another 2 to 4 hours. In the chronic animal the total fall for a similar dose is 2.5–3°C. The rate of cooling tapers off progressively until a temperature plateau is reached. This is then maintained for 15 to 30 minutes and passes over into a rise. Another nembutal injection promptly reestablishes the falling base line, which again, finally, turns upwards. Metrazol, a stimulant, conversely, sends the temperature up. Ether inhalation during the rising base line initiates a prompt but brief rise in brain temperature, some 0.05°C. within a minute or two, and then an even more precipitate fall to still lower values. By controlling ether administration after the nembutal fall has turned into a rise it is possible to hold the brain temperature fairly steady for hours—and most other observations were made against such a base line (Fig. 1). It is important to keep in mind that all vasomotor and other responses are obtained from a narcotized, and therefore depressed, brain.

The thermal changes in the brain are not a passive consequence of cooling of the entire body—due to muscular relaxation, cutaneous dilatation, and the like—for entirely similar changes in the brain are recorded when the "neutral" junction is placed in the abdomen or the aorta instead of in the usual constant temperature mixture. These drugs, therefore, depress brain temperature relative to that of the blood: indeed the temperature difference between them, in favor of the brain, may actually reverse under sufficient

narcosis. This probably accounts for the immediate warming produced by ether—a rapid vasodilatation temporarily masks the diminished brain heat.

Brain temperature diminishes under depressant drugs because its intrinsic heat production is lowered. Studies of oxygen utilization from circulating blood, indicate that this is decreased to one-third (Hou, 1926) or even one-tenth (Gayda, 1914) under anaesthesia. Changes in blood flow and temperature are, of course, additional factors (see below), but we are satisfied that the metabolic level of brain cells is most directly concerned. There is a close parallel, for example, between the temperature curve and depth of anaesthesia. As the brain begins to warm up the animal becomes more responsive to stimuli, may move spontaneously, and starts to "come out" of anaesthesia. Conversely, considerable sensory stimulation may initiate or accelerate the temperature rise.

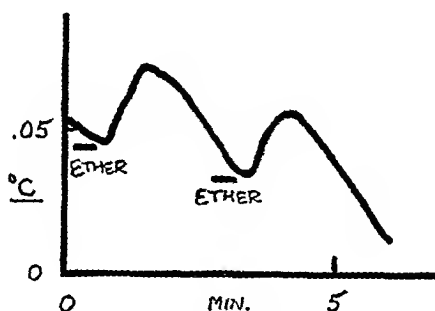


FIG. 1.

Aside from any interpretation, the brain temperature curve seems to offer an extremely sensitive and accurate index of the course of anaesthesia. It promises to measure the intensity, time-course, and locus of anaesthetic action, and experiments along these lines are in progress.

*Temperature gradients in the brain.* The only way in which it is physically possible for the brain to remain cooler than the blood is for heat loss from the head, by other routes than the blood stream, to exceed its local production. Over short time intervals, before equilibrium is established, warming the blood or cooling the brain will of course invert the usual relation; but at equilibrium, unless some other route of heat dissipation exists, this cannot remain the case. So long as any heat is developed in an organ, the blood must warm up in passing through it, for even when metabolism is fully in abeyance the tissue temperature will still be passively held at that of the blood circulating it—unless another route of heat loss exists. For the limbs, surface conduction and radiation constitute an impressive means of heat loss—the venous blood from a leg may be  $0.1^{\circ}\text{C}.$  cooler than the arterial, and be warmed  $0.1^{\circ}$  by placing a 60 watt lamp above the leg—and a similar situation, though less pronounced, might be anticipated for the head.

Actually a very definite temperature gradient exists within the brain, central regions being warmer than more surface ones by as much as  $1.4^{\circ}\text{C}.$  As a

thermoneedle is pushed from one parietal region to the other, temperature regularly rises and then falls. A similar rise occurs on penetrating from the vertex, sometimes ending with slight fall at the base (Fig. 2). The regularity of the change precludes its dependence on any particular structural pattern; and its symmetry about the midline eliminates any artificial cooling due to the small skull opening for introducing the needle. (A false gradient due to conduction of heat outwards along the shank of the hypodermic needle is excluded by this reversal of the gradient on crossing the midline; but as an extra check the needle sheath was withdrawn after placing the fine wire thermocouple and the same temperature gradient still appeared as this was later removed.)

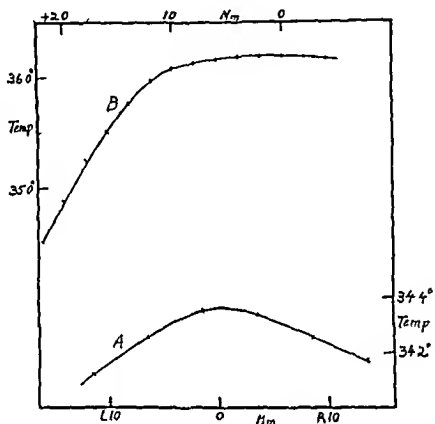


FIG 2 A Temperature curve in horizontal plane from left parietal cortex to right parietal cortex B Same in vertical plane from cortex to basal skull Abscissa—Horsley-Clark instrument setting

Clearly, then, the brain is continually cooled by heat loss through the skull and scalp; and possibly human hair has more than an aesthetic value, in helping to maintain brain temperature. That heat easily penetrates this vascular barrier, is shown by the considerable cooling of the brain that results from applying an ice bag to the head.

*Brain-blood temperature differences.* In unanaesthetized animals, Feitelberg and Lampl (1935) found the motor cortex as much as  $0.4^{\circ}\text{C}$ . warmer than the carotid blood. Under paraldehyde, the brain temperature fell to  $0.3^{\circ}\text{C}$ . below that of the blood stream. We have never observed such great temperature differences, but also find the brain to be warmer or cooler than the carotid blood, depending on anaesthetic level and degree of operative expo-

sure. The same is true for longitudinal sinus blood compared to that in the carotid. Extreme differences were, carotid  $0.037^{\circ}\text{C}.$  warmer to  $0.004^{\circ}\text{C}.$  cooler than sinus; brain  $0.034^{\circ}\text{C}.$  warmer to  $0.001^{\circ}\text{C}.$  cooler than carotid. When arterial blood and brain are at the same temperature, any rapid temperature change recorded from the brain cannot be due to vasomotor changes.

When the blood is warmer, a vasodilatation would cause a rise in brain temperature; when cooler, a fall. The former situation is deliberately induced by Schmidt and Pierson's (1934) cooled needle technique, the latter by Gibbs' (1935) heated needle one. By comparing the brain temperature change induced by a given stimulus under these various thermal relations it is possible to discriminate between the effect of vasodilatation and that of increased neural heat production. A control in point is the warming up of leg muscles, initially above arterial blood temperature, on stimulating the sciatic nerve.

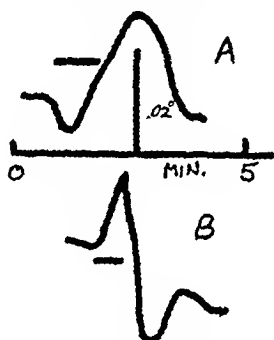


FIG. 3 A. Carotid occluded during signal. B. Same, but needle heated.

*Other controls.* At first the fine copper and constantin wires of the thermocouple were soldered to larger wires of the same metals where they emerged from the needle shank. It was found that temperature changes here set up potentials, presumably due to slight differences in composition, and later the fine constantin wire was continued to the cold junction and the fine copper ones to fixed copper connections in the permanent circuit which were well shielded from sudden temperature change.

The eyes were illuminated by a flash light or a 60 watt bulb. In the latter case a slow warming of the brain occurs over minutes; in the former, no direct heating action could be detected. In all the positive optic experiments such extraneous warming was excluded by controls with the eyes covered or with the thermojunction in non-optic regions.

The paw stimulation, when very vigorous, was found to cause a general blood pressure rise of 5 to 10 mm. Hg. as a maximum. The rise appeared promptly at the start and vanished as promptly at the close of the period of actual stimulation. No pressure change accompanied optic stimulation. A change in brain blood flow secondary to non-specific systemic effects is thus excluded as a cause of the localized thermal changes elicited by these stimuli.

Carbon dioxide excess and oxygen deficiency lead to vasodilatation in the

brain. During CO<sub>2</sub> inhalation and following a period of carotid occlusion, brain temperature rose (fell during occlusion). With the needle heated some 2°C., the same procedures caused a temperature fall (rise during occlusion). (Fig. 3) Clearly arterial blood was warmer than the brain in the first test, cooler than the heated brain and needle in the second, and the thermal changes were due to vasodilatation.

### SPECIFIC RESPONSES

*Optic.* With the thermocouple in optic pathways—lateral geniculate, radiations, or visual cortex—shining light in the eyes leads to a rise in temperature; other brain regions are negative. The rise is variable in duration, magnitude and form, depending on partially unknown variables; but in a sequence of tests made under essentially constant conditions there is good reproducibility. Fig. 4 shows the average of 35 positive experiments. The temperature rise begins 30–60 sec. after a 60 sec. period of illumination, reaches a maximum of 0.015°C. in 120 sec. and is over in 300–360 sec. Sometimes a secondary hump appears on the descending limb. In three experiments, light evoked a similar appearing temperature fall; and in 2 others a fall during stimulation preceded a rise following. These cases of heat loss must be due to vasodilatation and greater flow of blood that is cooler than the brain. The rise of temperature, however, cannot be similarly accounted for by increased flow of warmer blood, for in no case was a rise converted into a fall by heating the needle tip. The rise is, therefore, a consequence of increased heat production by the active neurons, though unquestionably modified by an increased blood flow when the brain is not at blood temperature.

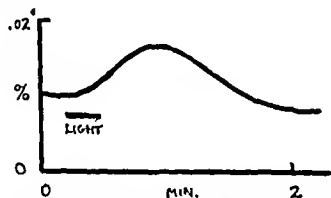


FIG. 4. Average curve from lateral geniculate body (A8, L8, +3.5) on illuminating eyes.

*Somaesthetic.* Stroking, pinching, and kneading the paw of the contralateral (mainly) fore leg causes a temperature rise in cutaneous radiations and cortex. The localization has been much less rigid than in the optic experiments, however, and occasionally quite generalized responses were obtained. Some characteristic records are reproduced in Fig. 5. While similar to the optic curves, these show a shorter latent period and more frequently begin with a negative dip. Further, it has proved possible to invert a heat curve resulting from paw stimulation by heating the needle tip. We conclude that



the major effect in this case is vasodilatation, though some increase in heat production is not excluded. Since most records of this series were made from tracts, nerve fibers with low metabolic intensity, and most optic ones from nuclei, cells and their connections with an intense metabolism, the differences are understandable.

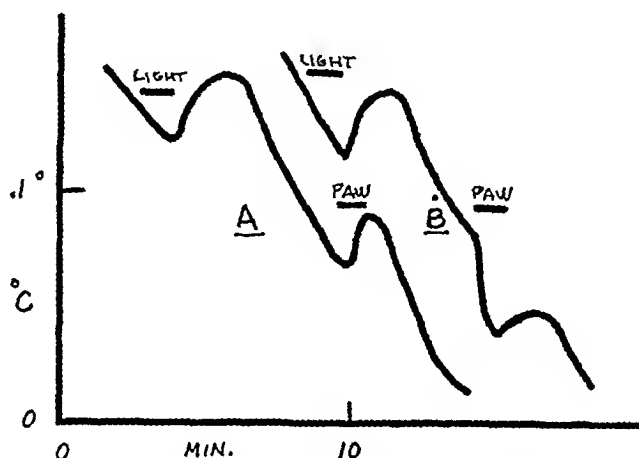


FIG. 5 A. Single responses to optic and to somaesthetic stimulation. B. Same, but needle heated. Note that only the somaesthetic response is inverted.

*Olfactory.* Blowing ammonia gas into the nostrils leads to a temperature rise in Ammon's horn. The maximum,  $0.01^{\circ}\text{C}.$ , is reached in about 100 seconds and the return to the basal level lasts another 150 seconds. With the needle heated, there is an initial cooling and a later warming. No responses were obtained in non-olfactory regions. The results indicate a combination of vasodilatation and increased neural heat production.

### DISCUSSION

A local control of brain blood vessels, by chemicals produced or consumed by cells in their immediate vicinity, has long been postulated (e.g., Roy and Sherrington, 1890); and direct evidence of an increased blood supply to an active brain region has been accumulating (Alexander and Revecz, 1912; Cobb and Talbott, 1927; Schmidt and Pierson, 1934. See the reviews by Wolff, 1936, and Gerard, 1938, for additional literature). The present findings further substantiate this view, as do the more detailed localization experiments of Santha and Cipriani (1938), performed since these were completed. Presumably  $\text{CO}_2$ , always produced by normal brain cell activity and a powerful dilatant, is the main agent for linking the increased food and oxygen supply with the increased metabolic need for them.

An evaluation of the active brain metabolism, itself, in terms of the temperature rise on receptor stimulation, is more difficult. The total duration of the increased temperature, 6 minutes, is reasonable for the delayed heat production of brain; but the tardy and slow appearance of the rise is contrary to

expectation. Possibly the cooling effect of an increased blood flow, which sets in promptly, is responsible for the slow rise; indeed the occasional presence of an initial temperature fall requires such an interpretation. Quantitatively, as discussed, brain temperature should rise some  $0.003^{\circ}\text{C.}$  per second of continued maximal activity, providing that no heat loss occurs and that the total heat produced over several minutes is summed. One minute's stimulation would produce almost  $0.2^{\circ}$ , the temperature rising progressively until the delayed heat is all developed. Actually, of course, heat is being steadily carried away and the initial temperature rise is delayed while the maximum is reached early and not maintained. The actual rise observed,  $0.015^{\circ}\text{C.}$ , is perhaps a reasonable resultant between extra heat production and continued heat loss.

### SUMMARY

A thermocouple placed by means of a Horsley-Clark instrument in determined structures of the cat's brain is used to record absolute temperatures and changes under anaesthesia or stimulation.

The brain loses heat through the cranial structures so that normally there is a temperature gradient from surface to interior, the cortex being  $1.4^{\circ}$  cooler than basal regions.

Because of this heat loss, the brain may be cooler than the blood reaching it, though normally it is warmer.

Anaesthetics (nembutal, ether) lower brain temperature (relative to that of the blood) and the temperature curve can be used to follow anaesthetic action

Optic stimulation causes a temperature rise only in the visual system of the brain; somaesthetic stimulation a rise, less sharply localized, in the cutaneous system; and olfactory stimuli in the olfactory one.

The temperature changes are due in part to extra heat produced by the active neurons, in part to local vasodilatation induced by metabolic products of these active neurons.

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# ON AN IPSILATERAL MOTOR EFFECT FROM CORTICAL STIMULATION IN THE MACAQUE MONKEY\*

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DURING stimulation of the motor and premotor cortex of the rhesus monkey (*Macaca mulatta*), under light ether or Dial anesthesia, with current pulses of low frequencies (from 2 to 4 per second) and of adequate shape and duration (Wyss and Obrador, 1937, Wyss, 1937) a typical ipsilateral response has been observed in the forelimb. The region of the cortex from which to obtain these effects lies on the border between areas 4 and 6 around the superior precentral sulcus. The ipsilateral response appears as a slow tonic movement including flexion of all fingers and flexion in the elbow and shoulder joint, and represents a movement of a smooth and even character even when elicited with a rate of stimulation as low as 2 per second. No intermittent contractions synchronous with the current pulses could be observed, as is the case in an ordinary response from the contralateral motor or premotor cortex.

This ipsilateral response in the arm was always accompanied by a contralateral complex movement either in the leg or in the arm depending on whether the (bipolar) electrodes were placed above or below the superior precentral sulcus. Especially in the latter instances the contrast in the type of contraction between the two sides was most striking, both effects starting after about the same latent period. Whereas at these low frequencies the contralateral response was a clonic progressive movement (described in a preceding paper as "premotor effect"), the ipsilateral one appeared to be a pure tonic contraction. No difference in the time excitability could be found between these two types of cortical response, the optimum current duration (rising phase for double condenser discharges) being for both from 10 to 20 milliseconds.

An analogous response in the ipsilateral leg was observed only once but was much less characteristic.

Ipsilateral effects from stimulation of the cortical motor and premotor areas of the macaque have been reported by several authors (for references see Bucy and Fulton, 1933). Recently a thorough analysis of the ipsilateral representation in the motor and premotor cortex of the monkey has been made by Bucy (1933) and Bucy and Fulton (1933). On stimulating near the superior precentral sulcus they usually obtained extension in the ipsilateral lower extremity although occasionally ipsilateral flexion occurred in the upper extremity. They also demonstrated, by the persistence of these ipsilateral responses after contralateral hemisection of the spinal cord as well as after removal of areas 4 and 6 of the opposite hemisphere, that these ipsilateral

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responses are independent of the contralateral responses and that their projection system most probably occupies the ipsilateral half of the nervous system.

The ipsilateral response described in this report seems to be identical with the ipsilateral flexion in the upper extremity obtained only occasionally in the work of Bucy and Fulton (1933). With an appropriate type of stimulating current it has been possible to demonstrate that the described ipsilateral response is quite different in character from an ordinary contralateral effect. It seems unlikely that such a *tonic* mechanism should serve as basis for a bilateral representation of volitional power in one-half of the cerebral cortex.

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# ON THE KINETICS OF RECOVERY DURING THE REFRACTORY PERIOD IN FROG'S NERVE\*

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SINCE THE refractory period is defined in terms of absolute or relative inability of stimuli to effect a response, it is evident that in theory, at least, it may also be defined in terms of the kinetics of the excitatory process as they are described, for example, by the strength duration curve.

According to most hypotheses of excitation, the excitatory states,  $p$ , produced in resting tissue by stimuli of equal durations but of varying strengths,  $V$ , vary as  $V$ , i.e.,

$$p = V \times \text{constant.} \quad (1)$$

In the writer's most recent analysis (Blair, 1936), for example,

$$p = \frac{KV}{h} (1 - e^{-kt}) + \frac{AV}{a} (1 - e^{-at}) \quad (2)$$

for rectangular stimuli, the  $A$ 's and  $K$ 's, large and small, being constants. When  $t$  is constant this reduces to equation (1).

It seems likely that during the refractory period one of the variables might be the rate of accumulation of the excitatory state per unit stimulus which is given by  $K$  of equation (2) on neglecting the second term of the right. This neglect does not affect the argument but it allows the use of  $K$  instead of a more complex expression with the same meaning (Blair, 1936). Another probable variable is  $h$  the threshold of  $p$ . There is no way, however, of distinguishing the separate variations of  $K$  and  $h$  but only of their ratio  $K/h$ . It will be convenient therefore, to let  $S$  denote the state of the tissue as it is described by  $K/h$ .

It will be observed that in equation (2) if  $t$  is constant and small enough that  $kt$  is small, a condition usually satisfied in refractory period measurements, the term  $(1 - e^{-kt})/h$  reduces to  $t = \text{constant}$  so that variations in  $h$  are undetectable. There is evidence in any case (see later) that  $h$  does not vary. Also the term in  $A$  and  $a$  which are probably physical factors, is probably constant when  $t$  is constant. Thus again using  $K$  to include also the terms in  $A$ , equation (2) reduces to  $\text{constant} = K V/h = SV = K_0 V_0/h_0$ , i.e.,  $KV/h$  will be a constant of value given by the resting value of  $K_0 V_0/h_0$  or

$$\text{constant} = KV/h = K_0 V_0/h_0. \quad (3)$$

Therefore, during the absolutely refractory period,  $V$  being infinite,  $S = K/h = 0$ , or, in other words, the conditions existing in the tissue either will not

\* Read at the Rochester meeting of the National Academy of Sciences, October 25-27, 1937.

permit the accumulation of an excitatory state at this time or the threshold  $h$  is infinite. During the relatively refractory period,  $K/h$  will increase from zero finally to attain its normal value,  $K_0/h_0$ .

The simplest kinetics to assume for the recovery of  $S$  from 0 to  $S_0$  during the relative phase are that the rate of recovery varies as the amount of recovery still to be made, or

$$\frac{dS}{dt} = \beta(S_0 - S) \quad (4)$$

$\beta$  being a constant, so that on integrating from  $S=0$ , at  $t=0$

$$S = S_0(1 - e^{-\beta t}). \quad (5)$$

or

$$\frac{K}{h} = \frac{K_0}{h_0}(1 - e^{-\beta t}) \quad (6)$$

But according to equation (3)  $Kh_0/K_0h = V_0/V$  so that

$$V_0 = V(1 - e^{-\beta t}) \text{ or } \log \frac{V}{V - V_0} = \beta t \quad (7)$$

$t$  being measured from the beginning of the relative phase. Experimentally, however,  $t$ , is usually measured from the beginning of the absolute phase, the duration of which may be represented by  $t_0$ . Therefore, the data from the present point of view should conform to the relation,

$$\log \frac{V}{V - V_0} = \beta(t - t_0). \quad (8)$$

Before testing the applicability of this relation, it will be convenient to consider the general description of the refractory period in terms of stimuli of equal durations. In Fig. 1 is given a representation of the usual experimental results. Under different conditions, two distinct types of curves, such as the upper and the lower, are obtained, and a third type which is a modification of the upper. The upper curve, which is perhaps the physiologically normal type will be called hereafter the curve of simple recovery.

The lower type of curve occurs after the tissue has been excised for some time, and in acid media, and under the influence of certain drugs and ions, (Graham, 1934). This curve descends transitorily below the value,  $V_0$ , of the initial stimulus and then returns rather slowly to  $V_0$ . The stage in which  $V$  is less than  $V_0$  is called the supernormal phase, but in reality it is usually subnormal with respect to the original fresh state of the tissue,  $V_0$  being greater than it was originally.

The other type of curve differs from the upper only in that it descends more rapidly in its initial stages. It does not appear that this type has been distinguished previously. The conditions for its appearance are not estab-

lished but may be either neutrality or alkalinity of the medium. The method of detecting it will be considered later. This type and the previous one with the super-normal phase will be called hereafter the curves of complex recovery.

*Simple recovery.* It is evident, on inspection of Fig. 1, that only the upper curve could possibly be represented by equation (8). This case will be considered now.

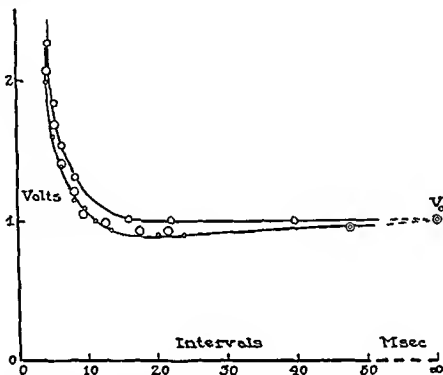


FIG. 1 The data of Table 1 by Adrian (1920, p. 18, Fig. 10) on the recovery of the frog's sciatic nerve at three different pH's. The abscissae are the intervals between the first stimuli at  $t=0$  and the second, which have strengths given by the ordinates,  $V$ . The ordinate,  $V_0$ , the initial and final least adequate stimulus, is arbitrarily given unit value for each curve. The upper curve is for pH 8.3, the lower two, large and small circles, respectively, for pH 6.8 and 6.5. If plotted in measured volts, the curves would coincide on the left, and the lower curves would be higher on the right. The second stimuli are applied at a different point on the nerve, so the refractory phase concerned is that left by the passage of the impulse.

Equation (8) is tested easily by plotting  $\log V/(V-V_0)$  against  $t$ . A straight line will be obtained if the equation is valid. Fig. 2 gives a number of cases of simple recovery in the sciatic nerve of the frog (measured by Adrian) plotted in this way. These curves are quite extensive, some going to  $V=16V_0$  and the shortest going to  $V=10V_0$ . In this type of plotting, the divergence on the right-hand side is large for small errors, and the divergence on the left is small for large errors. Therefore it is important, in denoting the validity of the equation (8), that the points fit closely to the line on the left the short-times end. The line cuts the time axis at  $t=t_0$ , the end of the absolute phase. The source of the data is given in the legend.

It will be seen that these data are linear in fair approximation. Another set, also by Adrian, is given in Fig. 3. These three curves are on the same preparation at different temperatures. The numerical data were published in this



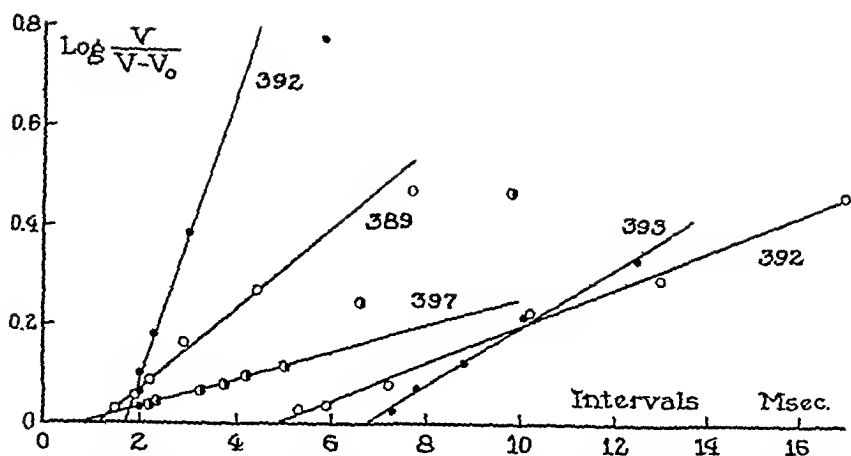


FIG. 2. Data by Adrian (1913) of simple recovery plotted according to equation (8). The lowest points in the diagram would be at about  $16V_0$  if the curves were plotted as Fig. 1. The curve on the left is probably complex, of the type of those in Fig. 4. The numbers on the curves are the page numbers of Adrian's paper.

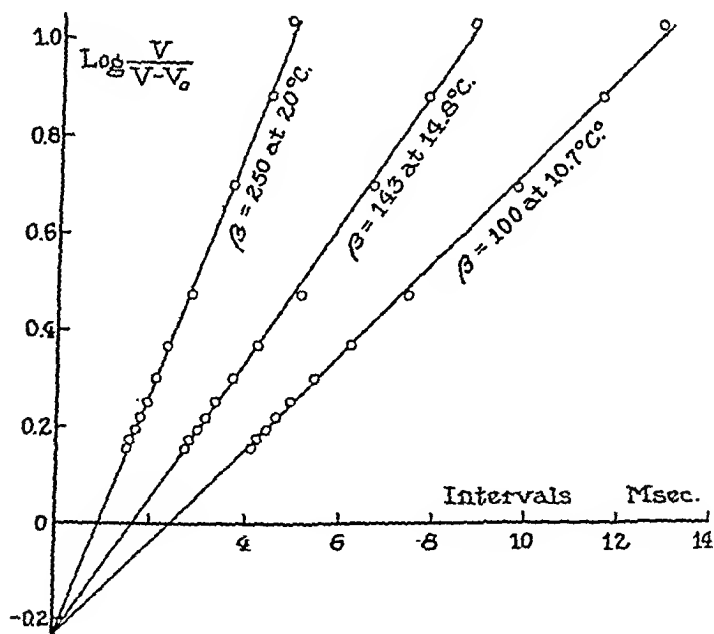


FIG. 3. Simple recovery on the same nerve at three different temperatures, as indicated; data by Adrian (1914; p. 460, exp. 1; p. 457, Fig. 1) plotted according to equation (8). The lines are extended to the ordinate axis to illustrate that the temperature changes both phases of the refractory period in the same ratio. The slopes of the lines are the constants,  $\beta$ , which are given below the curves. The real values, using natural logarithms, are 2.303 times as great as these.

case so they can be given more weight than those in Fig. 2 which were measured from graphs. In these cases, the conformance of the points to a linear relation is quite close throughout. Thus, the present results may be taken to indicate that the relatively refractory phase during simple recovery is defined by a state,  $S$ , of the tissue which is a measure of the ratio of the rate of accumulation,  $K$ , of the excitatory state per unit of stimulus to the amount of excitatory state,  $h$ , required to set off a response. The state,  $S$ , is zero at the beginning of the relative phase and builds up at a rate proportional to its displacement from the normal value,  $S_0$ .

*Complex recovery.* Of the complex recoveries, the type giving rise to the supernormal phase, as in the lower curve of Fig. 1, will be considered first. When this type is produced by acid in a tissue which gave previously the simple type, it is found (Adrian, 1920) that the curves for the two conditions tend to be coincident during the early part of recovery and that the supernormal state tends to be the same as the original normal state. That is, the supernormal phase of the lower curve (Fig. 1) would approach the upper curve without crossing it.

Therefore, in complex recovery, it may be said that the tissue sets out to recover to approximately the same point as it would in simple recovery, but that as it approaches this point some new effect enters to raise the threshold to a higher value (Adrian, 1920).

Considering now the kinetics of this type, it appears that the recovery tends initially to be given by equation (4), as before,  $\beta$  and  $S_0$  being approximately the same if the same tissue is used. In the later stages, however, it seems as if the end point,  $S_0$ , must have fallen slowly to a new level. If this variable end point,  $P$ , has kinetics also like equation (4), an initial value,  $S_0(1+b)$ , and a final value,  $S_0$ , it may be described by  $P = S_0(1+be^{-\gamma t})$ ,  $b$  and  $\gamma$  being constants and  $\gamma$  being small compared to  $\beta$ .

Replacing  $S_0$  in (4) by  $P$ , there is obtained,

$$\frac{dS}{dt} = \beta[S_0(1 + be^{-\gamma t}) - S] \quad (10)$$

and on integrating and replacing  $S$  by  $V$  as before and measuring  $t$  from the previous stimulus instead of the end of the absolute phase,  $t_0$ ,

$$\frac{V - V_0}{V} = e^{-\beta(t-t_0)} \left(1 + \frac{\beta b}{\beta - \gamma}\right) - \frac{\beta b}{\beta - \gamma} e^{-\gamma(t-t_0)}. \quad (11)$$

It can easily be seen that  $V = V_0$  when  $t = \infty$  and also when

$t = t_1 = \frac{1}{\beta - \gamma} \log \frac{\beta - \gamma + \beta b}{\beta b}$ . Also  $V$  is a minimum at the height of the super-

normal phase when  $t = t_2 = \frac{1}{\beta - \gamma} \log \frac{\beta - \gamma + \beta b}{\gamma b}$ . From these it follows on subtraction that

$$t_2 - t_1 = \frac{1}{\beta - \gamma} \log \frac{\beta}{\gamma}. \quad (12)$$

Therefore the relation of  $\beta$  to  $\gamma$  may be obtained by measuring the interval from the time when  $V$  first reaches  $V_0$  to the time when it reaches its minimum. If the data are frequent enough for large values of  $t$ ,  $e^{-\beta(t-t_0)}$  may be neglected in equation (11) and  $\gamma$  and  $\beta b/(\beta - \gamma)$  determined from a graph like Fig. 2. Data of this kind appear to be rare, but equation (11) may be tested in another way by data by Adrian (1920).

These data are given in Fig. 1 and table 1. As may be seen in Fig. 1 there are three curves, one simple and two complex. From the simple curve,  $\beta$ , was obtained by means of a graph like Fig. 2. Since the other curves coincide with this initially, when all are on the same voltage scale, it is indicated that this  $\beta$  will apply closely to them also. Using, therefore, this  $\beta$ ,  $\gamma$  was obtained from equation (12) and the other constant,  $b$ , by substitution. In table 1 are given the measured values of  $V$  and those calculated using the constants obtained in this way for all three of these curves. It will be seen that the agreement is fairly good.

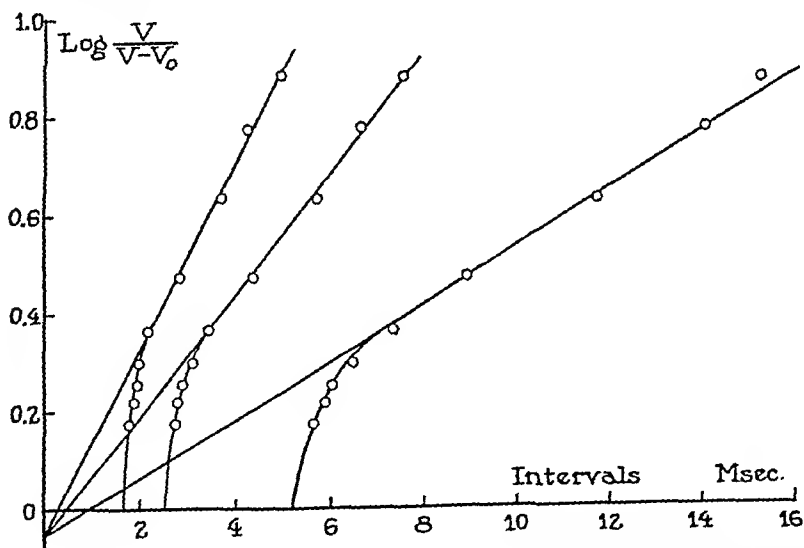


FIG. 4. Complex recovery in which  $\gamma$  is greater than  $\beta$ . The data, which are by Adrian (1914), are given in table 2. The three curves are at different temperatures. The curving downwards at the short-intervals end is due to the  $\gamma$  process. Adrian's Fig. 2, p. 458, gives a set of similar curves.

In the other complex form of recovery, since there is no supernormal phase, the complexity is not immediately apparent. If the data are plotted according to equation (7), however, the results are quite different from Figs. 2 or 3. In Fig. 4 are plotted a set of data by Adrian (1914) of this kind. The curves are linear for long intervals, but for short intervals the points fall rapidly. Since

the slopes of the lines are about the same as those in Fig. 3, it is immediately suggested that they again measure the constant  $\beta$ . But the falling away of the points at the short-intervals end suggests the addition in this phase of a much faster reaction than the  $\beta$  reaction. This suggests in turn that if the previous basis, equation (10), is still applicable, the constant  $\gamma$  has now become large rather than small compared to  $\beta$ . If this is the case, the term in  $\gamma(t-t_0)$  in equation (11) may be neglected at long times so that this equation becomes,

$$\log \frac{V}{V - V_0} = \beta(t - t_0) + \log \frac{\gamma - \beta}{\gamma - \beta - \beta b} \quad (13)$$

which predicts lines of slope  $\beta$  as required for Fig. 4. Fig. 4 is plotted with  $t$  instead of  $t-t_0$ ; therefore when  $t=t_0$ , the point on the time axis to which the diverging points at the short-times end are directed, the ordinate of the line is

$$\log \frac{V}{V - V_0} = \log \frac{\gamma - \beta}{\gamma - \beta - \beta b}.$$

This point,  $t=t_0$  can be obtained fairly closely by inspection and more closely by trial. This is assisted in the present case by the circumstance that the set of data consists of three curves at different temperatures. For Adrian observed that on lowering the temperature, all phases of the refractory state, including the absolute period, are prolonged in the same ratio. Thus in Fig. 3, for example, the lines come together at a point on the axis,  $t=0$ . The lines in Fig. 4 for the long intervals meet similarly. Also there must be a point lower down on the axis,  $t=0$ , at which lines from each of the lowest points at the short-times end meet after cutting the axis of abscissae at  $t=t_0$ . Therefore, if one absolute period is determined closely, the others can be obtained by this means.

Having obtained  $t_0$  and  $\log \frac{\gamma - \beta}{\gamma - \beta - \beta b}$  as indicated, and  $\beta$  from the slopes

of the lines,  $\gamma$  may be calculated from the data of short durations, using equation (11). In table 2 are given the data of these curves as observed and as calculated according to equation (11). There are some disagreements for the short intervals, notably the first point of the third curve, which is 12 per cent too high. The voltage changes very rapidly with time in this region, however, because the voltage-time curve rises very steeply, and actually this divergence corresponds to only 0.02 msec. or about 0.5 per cent in time, which is well within the experimental error. The agreement in the less sensitive regions of the curves is entirely satisfactory.

It appears, therefore, that the kinetics of complex recovery are represented adequately by equation (10), which may be pictured schematically as in Fig. 5. Here on the left is the case of simple recovery:  $b=0$  so that the state,  $S$ , starting at zero at time,  $t=t_0$ , the end of the absolute phase, returns to its

final resting value,  $S_0$ , at a rate proportional to the distance it has yet to go. In the complex types of recovery, the one with a supernormal phase is represented in the middle. In this case, the end point,  $S_0$ , is not fixed but, starting at an initial value,  $P$ , descends exponentially rather slowly to a final level,  $S'_0$ . The time constant of this process is  $\gamma$ . The state,  $S$ , recovers as before at a rate proportional to the distance to the end point. But since the time constant,  $\beta$ , of this process is greater than  $\gamma$ ,  $S$  transitorily exceeds  $S'_0$ . In the other type of complex recovery,  $\gamma$  exceeds  $\beta$  so that as indicated in the right-hand side of the figure, there is no supernormal phase, but the recovery of  $S$  in its later stages is too slow to be in keeping with its rate at the beginning.

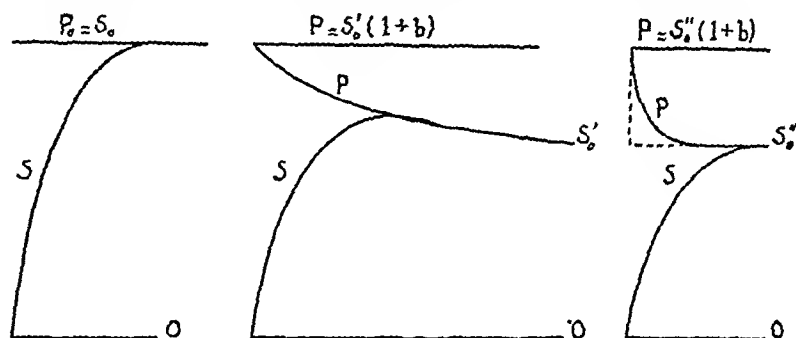


FIG. 5. Illustrating from left to right, respectively, simple recovery, complex recovery with the supernormal phase ( $\gamma$  small), and complex recovery with  $\gamma$  large. In the complex cases, the upper curves are those of the  $\gamma$  process, which the  $\beta$  process, or the state,  $S$ , approaches as end point. The reciprocals of  $S$  give the curves of the stimuli like Fig. 1. On the right, the area between the dotted coordinates and the curve of the  $\gamma$  process gives the recovery oxidation according to the hypothesis in the text.

It is not at all probable that, as shown in Fig. 6, the initial end points  $P = S_0(1+b)$ , are the same for the same tissue under different conditions. This is approximately true, however, in the set of data of Fig. 1 and table 1, but in these cases  $b < 1$ . For the set in table 2, however,  $b = 8$ , approximately, so that  $S_0(1+b) = 9S_0$ . Therefore, in these cases,  $S_0$  would be much lower than normally, or the threshold  $V_0$  much higher if  $S_0(1+b)$  were unchanged from that occurring in the tissue in the normal state.

The question arises at this point as to why the  $\gamma$  process does not appear in simple recovery. The obvious assumption to be made is that it does not exist, but this is neither likely nor necessary because it will be seen in equation (13) that if  $\gamma$  becomes increasingly large compared to  $\beta$ , or if  $b$  becomes small, the second term on the right will approach 0. Therefore a case of recovery in which  $\gamma$  is very large or  $b$  small will appear to be simple unless the data are obtained very early in the relative phase. And in fact, in several of the curves of Fig. 2, the first point tends to fall below the line, indicating that the  $\gamma$  process existed and was still incomplete at this stage. Therefore, it seems probable that all recovery is representable by equations (10) and (11)

and that simple recovery is but a special case of the kind outlined above. A possible reason for the smallness of  $b$  will be given later.

*The factors affecting the constants.* The data of Figs. 3 and 4 were taken by Adrian (1914) to determine the effect of temperature. As was remarked above, he discovered that all phases of recovery were altered by temperature in the same ratio. This is illustrated in Fig. 3 by the circumstance that all three of the lines meet at a point on the ordinate axis. The slopes of the

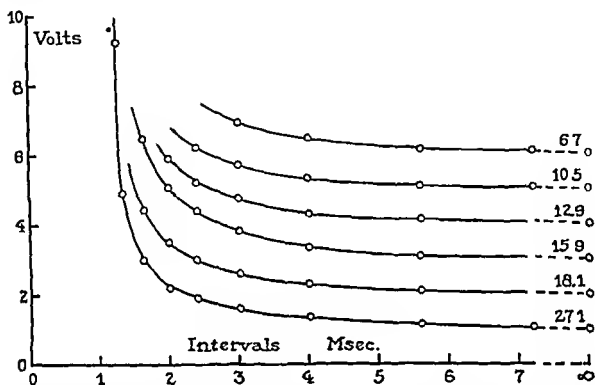


FIG. 6 The data of Blair and Erlanger (1931, p. 548, Fig. 12) on the refractory phases of different fibers in a small trunk having impulse velocities in meters per second, as indicated by the numbers on the curves. The abscissae are the intervals between the stimuli. The ordinates are volts on a scale on which the value for infinite interval is unity. The zero for each curve is the point at infinity of the curve next below. The three curves for which no point at 7.2 msec. is given were slightly supernormal in this region. This was ignored and the value of  $V$  at 7.2 msec. was taken for the value at infinity. Therefore these three curves should be slightly lower on the left side.

lines, the constants  $\beta$ , go in this case from 100 at 10.7°C. to 250 at 20°C., increasing about 2.7 times for a 10° rise in temperature. (The average of Adrian's results (1914, p. 463) is nearer 3.0.)  $\beta$ , therefore, is a function of temperature. According to Adrian's finding, and as is illustrated in table 2,  $\gamma$  also is the same function of the temperature with the same coefficient. The constant,  $b$ , according to table 2 is almost independent of temperature. There is no assurance from these data, however, that this process does not extend back into the absolute phase; so all that they indicate is that the value of  $b$  at the beginning of the relative phase is independent of temperature. There is other evidence, however, that the process does begin at the beginning of the relative phase (see later).

With respect to pH,  $\beta$  is independent according to table 1, but  $\gamma$  is decreased very greatly on increase of acidity, as also is  $b$ . It appears that  $\beta$

tends to be independent of fiber size, according to the data of Blair and Erlanger (1933), who determined the refractory periods of several fibers in the same trunk along with the nerve impulse velocities. They concluded that both the absolute and relative phases increased considerably as the velocity decreased. On replotting their Fig. 12 (p. 548) in Fig. 6 here so that the curves for all the fibers are on the same scale, it is evident, however, that the curves for all the velocities are about the same shape and that the absolute periods are also about the same. Since  $\beta$  determines the shape of these curves, it appears that  $\beta$  does not change markedly with the velocity and therefore with the fiber size. This conclusion is probably not general, however, because in the velocity range of these data, the duration of the rising phase of the action potential changes rather little (Blair and Erlanger, 1933, Fig. 18, p. 553) with the velocity. But the absolute refractory period, at least, must increase with the low velocities for which the duration of the rising phase and therefore of the spike of the action potential is greatly increased, since it is agreed (see later) that the absolutely refractory period has about the same duration as the spike. It appears, however, that fibers with velocities in the range considered here can carry approximately the same number of impulses per second despite their differences in velocity because the recovery times are approximately equal. This property may serve some physiological purpose.

*Additional relations.* There are a number of additional observations concerning the refractory period which should be of use in attempting to interpret the kinetics of recovery. These will be considered now.

An important property of the supernormal phase has been determined also by Adrian (1920, p. 18, Fig. 9). This phase may be sufficiently long and stable so that during it a strength-duration curve may be taken. Adrian found that such a curve differed from that taken during complete recovery only in that it was lower throughout by a constant ratio of the ordinates. This means, in terms of equation (2), that only  $h$  or  $K$  or  $K/h$  has been altered, the constant,  $k$ , remaining as before. Therefore the assumption above of  $K/h$  as variable,  $k$  being constant, is justified experimentally for the supernormal condition. But since the supernormal condition is only a particular stage in the growth of the state,  $S$ , it is indicated that  $K/h$  is the only variable for all stages of  $S$ . In any case, the variations of  $k$  are probably small enough so that they have no effect, for the reasons given earlier.

Another observation of Adrian (1921) is that the absolutely refractory period and the duration of the spike of the action potential are approximately equal. Gasser and Grundfest (1936) agree with this conclusion.

The after-potential of the action potential which is associated with and disappears with the supernormal phase (Gasser and Erlanger, 1930) is considered by Gasser and Graham (1932) to be a manifestation of some process independent of that giving rise to the spike. This process is oxidative or gives rise to an oxidative process because the excess oxygen consumption per response on stimulation tends to vary approximately with the magnitude of the after-potential when it is greatly exaggerated by drugs (Schmidt, 1933;





Schmidt and Gasser, 1933; Gasser, 1934, reviews this point of view). The after-potential, being associated with the supernormal phase, is therefore associated also with the process of time constant,  $\gamma$ . It appears probable, therefore, that this  $\gamma$  process is oxidative. That  $\gamma$  increases with alkalinity is consistent with this view since the rates of oxidative processes in tissue increase with alkalinity.

It will be observed incidentally in these regards that when  $\gamma$  is large, as in table 2, the negative after-potential will be so close to the spike and over so quickly that it will be distinguishable with difficulty, in accord with common experience.

Now if the process of time constant,  $\gamma$ , is an index of an oxidative process, the question arises whether or not it measures its rate directly. If it does, then will the area under the curve of the  $\gamma$  process measure the amount of recovery oxidation. The area concerned will be that, for example, between the dotted coordinates in the right-hand side of Fig. 5 and the curve above it. As can easily be seen, the area under this curve is,

$$\int_0^{\infty} S_0 b e^{-\gamma t} dt = \frac{S_0 b}{\gamma}. \quad (14)$$

Therefore, according to the hypothesis,  $bS_0/\gamma$  measures the amount of oxidative recovery. But if this is true, it is to be expected that this quantity will remain approximately constant as  $\gamma$  varies, for it is not likely that the energy for recovery will be very different in different cases, so long as the factors producing them are not extreme. In table 2, for the 15°C. case,  $\gamma = 5800$ , and  $b = 8$ , so that  $b/\gamma = 0.0014$ . In table 1, the supernormal curve at pH 6.5 and at 12.5°C.,  $\gamma = 42.5$ ,  $b = 0.16$ , and  $b/\gamma = 0.0038$ . Therefore, in spite of the great difference in  $\gamma$ , the quantity  $b/\gamma$  is of the same order of magnitude in these two nerves which are at approximately the same temperature. Presumably,  $S_0$  is not greatly different; so the areas under the curves are about the same. It seems probable, therefore, that the  $\gamma$  process is a transient excess of the rate of some oxidative process above its resting value. And the extent to which it has proceeded is a measure of the state of oxidation which it has produced. This matter is discussed by Gerard (1932) and related to the heat production which he found to be of the same mathematical form as that assumed for the  $\gamma$  process.

With respect to the variation of  $b/\gamma$  with temperature in Fig. 5,  $b = 8$ , approximately, for all three curves, or, in other words, the oxidative rate, after a response, is increased by the same fraction of the basal rate at all temperatures, but  $\gamma$  is more than three times at large at 20° as at 10°. Therefore, since  $b/\gamma$  is one-third as great it must be assumed that only one-third as much recovery is necessary at 20° as at 10°, providing  $S_0$  is invariable with temperature. There is no information on the dependence of  $S_0$  on temperature in these data, but it can be shown that as the temperature is varied, keeping the duration of the stimulus constant,  $h_0 = K_0 V_0$ , approximately. But  $h_0/K_0$  decreases somewhat as the temperature increases (Blair, 1935, p. 310).

Therefore  $S_0$  increases with temperature. The increase is probably slower, however, than the decrease of  $b/\gamma$ . Therefore, according to the present hypothesis, the nerve will recover more economically at higher temperatures as far as the process of time constant,  $\gamma$  is concerned, i.e., there will be less oxidative recovery per nerve impulse. This may not apply to the total energy however. For the  $\gamma$  process may be operated from an oxidative reserve, and the replenishing of the reserve may be more expensive under one condition than another.

*The absolute period.* The only direct information on the absolute period from these data is Adrian's observation that its temperature coefficient is the same as that of the relative phase. That is, when temperature alone is varied,  $\beta t_0 = \text{constant}$ , and also  $\gamma t_0 = \text{constant}$ . When the pH is varied, however, both  $\beta$  and  $t_0$  remain constant but  $\gamma$  varies greatly. It appears, therefore, that if there is any association at all,  $\beta$  and  $t_0$  are related, but  $\gamma$  and  $t_0$  may be quite independent. The relation of  $\beta$  to  $t_0$  suggests that these factors depend in turn on the same property of the system. Therefore, if the nature of the  $\beta$  process becomes known, the nature of the absolute phase may become apparent, or vice versa.

It was concluded by Adrian that in his experiments the strength of the initial shock did not modify the recovery even in the cases in which this was measured at the same place. This may not always be true, however, according to the results of a number of investigators. Erlanger and Blair (1931) and Blair and Erlanger (1933), for example, have investigated the effect of shocks of either polarity given in the absolute period on subsequent recovery. It appears that a shock from the cathode during the absolutely refractory period increases the absolute period without modifying the curve of the relative period (1933, p. 546). The effect of the anode (1931, p. 125) is not determinable unambiguously from the data given, but it may be the reverse. The observation that the cathodal shock prolongs the absolute period, and other considerations, led Erlanger and Blair (1931) to postulate that the relative phase is the disappearance of what they call the postcathodal phase of depression, following the action current spike as stimulus. This idea is used also by Rashevsky (1933) and Monnier (1934). It will be referred to later.

*The nature of the processes.* It is evident that a possible interpretation of the  $\gamma$  process is as follows: at the beginning of the relative phase, the rate of some oxidative process is found to have a value,  $S_0(1+b)$ , and this rate subsides exponentially to a value,  $S_0$ , which is the resting metabolic rate of the tissue. In an acid medium or in other media giving rise to a supernormal phase of recovery,  $b$  is usually small, i.e., the rate of oxidation at the beginning of the relative phase is not much above the resting value,  $S_0$ ; therefore recovery takes a long time and the subsidence of the oxidative rate of the resting level is slow, i.e.,  $\gamma$  is small. In an alkaline medium  $b$  is large, i.e., the oxidative rate at the beginning of the relative phase is much above the resting rate. Recovery, therefore, takes place rapidly, and the resting rate,  $S_0$ , is soon attained, i.e.,  $\gamma$  is large. The total excess oxidation is perhaps usually

about the same in both acid and alkaline media. But there are cases, simple recovery, in which it appears, as was mentioned above, that  $\gamma$  is unusually large or  $b$  is unusually small so that  $b/\gamma$ , the oxidative recovery, is small. This may be a property of fresh preparations in which recovery may be very economical, or it may be that recovery is accomplished by a different method. And there are other cases of the opposite kind in which, under the action of drugs, the supernormal phase is very prolonged, *i.e.*,  $\gamma$  is extremely small and  $b$  is probably large so that  $b/\gamma$  the oxidative recovery, is unusually large (Schmidt and Gasser, 1933).

Since the  $\gamma$  process has an electrical sign, it is implied in the above conclusion that the resting metabolic rate,  $S_0$ , or the factors which determine this rate, may determine also the resting membrane potential. Therefore, since the negative after-potential accompanying the  $\gamma$  process is a lowering of the membrane potential, it is indicated either that an increase in the rate of oxidation involves a decrease in the membrane potential, or that a lowering of the membrane potential brings about an increase in the rate of oxidation. The latter alternative is the more probable, however, because the membrane potential is low on asphyxiation and recovers with oxygen (Furusawa, 1929; Gerard, 1930, 1932, p. 510) indicating that the state of oxidation determines, or is related to, the membrane potential. Also, in asphyxia (Amberson, Parpart and Sanders, 1931) the after-potential becomes less and less evident. This may be because it disappears very slowly, if at all, since the oxidative process required to reduce it is absent, and the membrane potential becomes progressively lower. Therefore it appears likely that the membrane potential during the  $\gamma$  process is low because the state of oxidation is low, and because the state of oxidation is low the rate of oxidation is excessive until the state of oxidation is brought back to normal.

The  $\beta$  process is independent of the  $\gamma$  except that its end point is determined from moment to moment by the stage which the  $\gamma$  process has reached. In accord, therefore, with the assumption above that the  $\gamma$  process is oxidative, the rate of oxidation, or the factors which determine this rate, determine also the extent to which the  $\beta$  process will proceed. It scarcely can be considered that this process has any part in restoring the membrane potential since it apparently has no electrical manifestation, and particularly since it does not start until after the action potential spike has subsided, *i.e.*, until the membrane potential has returned to, or nearly to, its normal value. It appears, therefore, that this  $\beta$  process involves only the restoration of the ability of the tissue to respond to stimuli. Thus the excitability is a property which is added, to, or is recovered by, the system after it has regained in large part, at least, the organization which determines its potential.

At present, there does not seem to be any conclusive evidence either from the data of excitation or of recovery to indicate the nature of the quantity  $K/h$  and therefore of this  $\beta$  process. It cannot be defined any further, therefore, than as a return of excitability in this particular sense.

It may be suggested, however, that the excitability-substance of Osterhout

and Hill, (1933) is involved. For if this occurs in nerve and is lost by the irritable structure during the response the  $\beta$  process may be the reacquisition of this substance by the membrane or its recombination with the elements of the membrane.

*The relation of  $\beta$  and  $\gamma$  to the time constants of excitation.* It is inconsistent with present considerations to assume that the constant,  $k$ , of equation (2) the excitability in the usual sense, is related to  $\beta$ . Furthermore,  $k$  changes markedly with the velocity of the impulse (Erlanger and Blair, 1933; Blair, 1934) in the range in which  $\beta$  does not, according to Blair and Erlanger (Fig. 6 above). The numerical value of  $k$  is greater also, being several thousands instead of hundreds for the frog's sciatic nerve. It is similarly unlikely that  $k$  is related to  $\gamma$  since  $k$  is much less dependent upon pH. There seems to be a possibility, however, that  $\beta$  and  $\gamma$  are related to the time constant of inhibition (Rashevsky, 1933), or accommodation (Monnier, 1934; Hill, 1935). The reason for assuming this possibility is as follows: if the oxidative process during recovery is associated with an alteration of the membrane potential, it is very probable that an inadequate electrical stimulus, or any stimulus before it becomes adequate, which will change the membrane potential, will also in consequence disturb the resting oxidative equilibrium and initiate a  $\gamma$  process. This, in turn, should bring about a  $\beta$  process leading to a new state,  $S_0$ , corresponding to a new value of  $K/h$ . Therefore, during stimulation it may be necessary to take into account these factors which may be the same as inhibition. Since this matter can be investigated experimentally, however, it will serve no useful purpose to speculate upon the nature of the relations until the appropriate data are available. The observation of Blair and Erlanger (1931) that the postcathodal depression and the relative refractory phase disappear in about the same times is very suggestive that  $\beta$  determines both, but it is obvious that the dependence of  $\gamma$  on pH will allow a rather large variation in the experimental results; so from this point of view their results are special cases. There is another difficulty, too, that the postcathodal depression does not always occur in frog's nerve and muscle (Blair, 1936); whereas the refractory phase and presumably, therefore, the  $\beta$  process always does.

*The negative and positive after-potential.* It will be evident that recent work on the after-potentials particularly of mammalian nerves (Gasser and Grundfest, 1936) (Lehmann, 1937) requires a more complex representation than has been given. For in these nerves the composite of after-potential phenomena is oscillatory, consisting of a negative potential followed by a positive then by a negative and so on, resembling a damped mechanical oscillation of increasing period. The excitability is super- and sub-normal in step with the negative and positive variations. It is evident, therefore, that the representation of the  $\gamma$  process as a simple exponential while adequate except under special conditions in the frog will be inadequate with mammalian nerve. In this case the  $\gamma$  process must be represented by some appropriate oscillatory function, or as suggested by Gasser and Grundfest (1936), by two contrary processes.

These cases are so complex mathematically in relation to the accuracy of measurement that it seems likely that they can be studied most safely as extensions of the simpler situation in the frog.

### SUMMARY AND CONCLUSIONS

It appears likely that by means of stimuli of short, equal durations and variable strengths one is enabled to describe the refractory period in terms of, and only in terms of, the ratios,  $S=K/h$ ,  $K$  being the rate of accumulation of the excitatory state per unit stimulus and  $h$  being the threshold value of the excitatory state. At the end of the absolute phase, this state,  $S$ , beginning at 0 returns to its end point,  $S_0$ , at a rate proportional to the distance remaining. The end point, however, depends upon the rate of some oxidative process which is raised by the response, and which recovers exponentially to its resting value. When its recovery is fast there is no supernormal phase of excitability, but when it is slow there is a supernormal phase as well as an evident after-potential which is associated in some way with the excess oxidation. The time constant of the recovery of the state,  $S$ , has no electrical manifestation, is independent of pH, and of fiber size to some extent, is increased about three-fold with  $10^\circ\text{C}$ . rise in temperature, and varies inversely as the absolute period as this varies with temperature. The time constant of the oxidative process varies similarly with temperature but is increased very greatly on going from acidic to alkaline media. If both of these processes are chemical, a method is provided for studying the reactions concerned with much greater accuracy than is ordinarily possible. In any case, the mode of variation of the time constants of these processes with different reagents and conditions should throw considerable light on the nature of the excitatory mechanism and of the refractory state.

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# FUNCTIONAL RECOVERY IN OCULAR MUSCLES OF A CHIMPANZEE AFTER SECTION OF OCULOMOTOR NERVE\*

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## I. INTRODUCTION

THE MORPHOLOGICAL changes which take place during degeneration and regeneration of peripheral nerves have been thoroughly investigated (Ranson, 1912; Ramón y Cajal, 1928; Speidel, 1935). In the case of the cranial nerves, however, information is less complete and little attention has been given to the functional aspects of the problem, especially with regard to the return of motor power following transection. Highly favorable for such a study are the muscles of the eye. The movements of the two eyeballs are synchronous and coördinate, and any differences in their coördinated actions, or in the movements of the eyelids, are therefore conspicuous. The present note is based upon study of a chimpanzee following section of the third cranial nerve. The characteristics of the oculomotor paralysis were analyzed in detail as well as the stages of regeneration and recovery of function.

## II. OBSERVATIONS

Details of these observations are included in the following protocol:

*Experiment 1. Section of right IIIrd cranial nerve in chimpanzee; complete ophthalmoplegia; "fright" reaction after 5 weeks; gradual recovery with disappearance of ptosis after 3 months and return of conjugate movements. Stimulation of left eye fields causing elevation of right lid and movement of eyeball; section of regenerated nerve abolished cortical response. Ablation of eye field. (Tim)*

The subject of the experiment was a male chimpanzee in which a small flocculonodular lesion of the cerebellum had been made 6 months previously (Dow, 1938).

*First operation.*—On February 5, 1937 with the animal under deep sodium amytal anesthesia the right oculomotor nerve was exposed by elevating the right temporal lobe and cleanly severed with a pair of sharp scissors. The two cut ends lay separated from one another by 2 to 3 mm. after the transection. The cortical eye fields were in no way damaged by the operation.

*Postoperative notes—1st day.*—When the animal recovered from anesthesia, the right eye showed complete ptosis, the globe was externally deviated, the pupil maximally dilated (7 mm.), and "fixed" to all types of light stimulation; the only slight orbital movement detectable was in the horizontal plane between the outer canthus and (partially) the midline (IVth and VIth nerves). Both eyelids moved downward in response to corneal and visual stimulation and during spontaneous blinking.

*5th day.*—The animal had now quite recovered from the operation. Movements of the right eyeball between the outer canthus and central visual axis were more evident. Ptosis continued to be complete.

*11th day.*—The ptosis began to disappear; the right palpebral fissure being open 1.5 mm.; and by the 29th day (March 6) it was 4 mm. wide. Recovery developed more rapidly on the temporal than on the nasal side of the eyelid.

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31st day—The animal had been tested several times previously for the "fright" reaction with indefinite response. Today when threatened the right fissure within about 30 seconds widened to 9 mm, remained open for 45 seconds and then narrowed down to 4 mm. This raising of the upper eyelid associated with fright, and termed the "fright" reaction (Bender, 1938), was thus demonstrated and it proved entirely similar to the corresponding phenomenon observable in ophthalmoplegia in monkeys.

54th day—Ptosis was still diminishing, the palpebral fissure being open 8 to 9 mm as indicated in Fig 1. Note that the left eyeball is looking upward.



FIG 1 Photograph taken on 54th day after section of right oculomotor nerve. Note partial recovery from ptosis of right eye (open 8 to 9 mm). The left eye is looking upward indicating that the right must be maximally opened.

60th day—*Pseudo Graefe phenomenon*—During the period in which the ptosis had been diminishing it had been noted that the right upper eyelid did not move in unison with the normal left eyelid, thus, when the chimpanzee looked down, the left lid moved downward, whereas the right superior lid remained stationary. This phenomenon was especially noticeable today (April 6), when the affected palpebral fissure was open 10 mm. By the 81st day (April 27) it was noted that when the left eye looked down\* the right upper eyelid definitely became slightly elevated (pseudo Graefe phenomenon, Fig 2). The latter movement was evidently due to active contraction in the recovered levator palpebrarum muscle.

*Subsequent course*—After the 81st day recovery of function proceeded continuously, ptosis was less marked, the pupil became smaller (6 mm) in diameter, and the eyeball made movements toward, but not beyond, the vertical plane of the central visual axis. This is well illustrated in photographs taken on the 102nd day (Fig 2, A and B). On the 110th day (May 26) it was noted that when the eyes were conjugately deviated to the left, the right eyeball moved to the left beyond the central visual axis, thus demonstrating the presence of contraction in the right internal rectus muscle. The right pupil measured 5 mm in diameter. On gazing to the left or downward, the right upper eyelid was found to retract, i.e., impulses to the right internal or right inferior rectus were accompanied by impulses to the levator palpebrarum. In other words, several muscles innervated by the formerly cut oculomotor nerve contracted simultaneously, and the levator palpebrarum contracted when it should have relaxed. In order to ascertain whether these contractions

\* When the chimpanzee looked down only the left eyeball rotated toward the lower lid edge. Vertical movements in the right globe were not apparent, probably because the depressor and elevators of the eye contracted simultaneously. Proof that this was the case was found in a monkey in which the inferior rectus muscle was divided and the oculomotor nerve cut. When regeneration appeared, upward and inward movements of the eyeball and simultaneous retraction of the lid occurred.



en masse were related to the oculomotor nerve regeneration, stimulation of the eye center in the cerebral cortex was carried out. Horizontal movements of the globes, if thus induced (in which the right internal rectus muscle would take an active part), should be accompanied by a retraction of the right upper eyelid. The assumption was that the cortical stimulus directed to the internal rectus would be conducted along the regenerated oculomotor nerve to the levator and other ocular muscles.

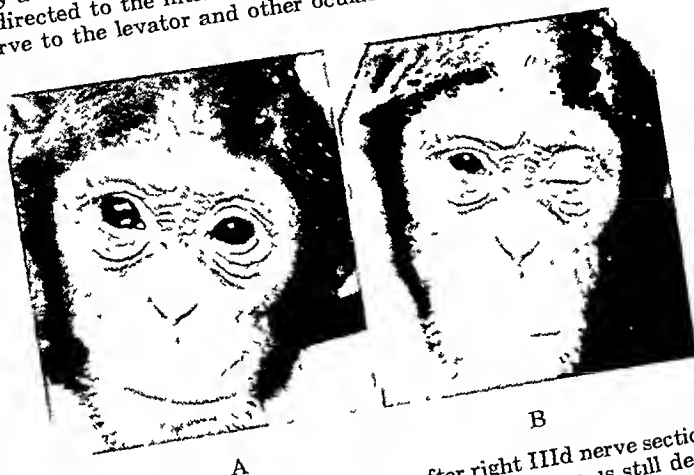


FIG. 2. Photographs of eyes on 102nd day after right IIIrd nerve section. A. Complete recovery from ptosis in right eye. The right eyeball, however, is still deviated outward. B. The pseudo-Graefe phenomenon: the left eyelid descends in looking down but the right upper eyelid remains contracted and right globe moves slightly toward the midline.

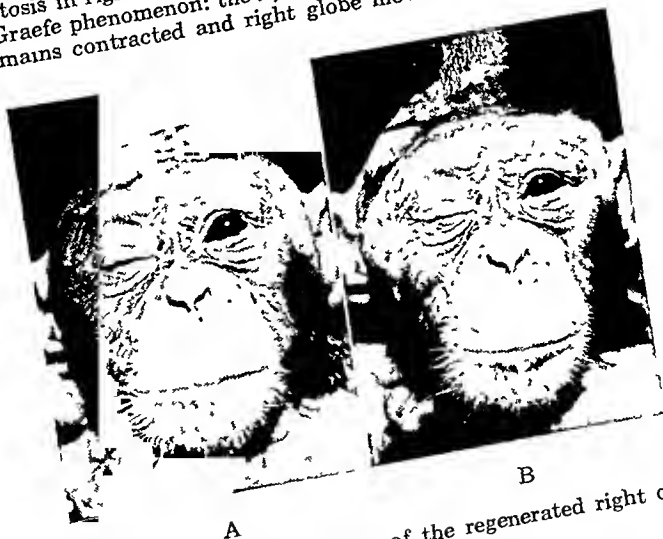


FIG. 3. Return of ptosis after resection of the regenerated right oculomotor nerve. A. Looking upward. B. Looking straight ahead.

*Second operation—Stimulation of cortical eye fields (Area 8).*—On May 26, 1937, under ether anesthesia, the right and left cerebral hemispheres were both exposed and various points, particularly those of the eye fields, stimulated (see Fig. 3) with faradic current, and also by the Wyss and Obrador (1937) double condenser stimulator. Observations on the effects of stimulation were made before and after section of the reunited oculomotor nerve. Bipolar and unipolar electrodes were both used.

*Third operation—Resection of the right III<sup>d</sup> nerve*—After the eye fields had been stimulated the right oculomotor nerve was again reexposed and found firmly reunited, it was again severed with scissors. Thereafter the animal again developed complete ptosis of its right eye (Fig 3, see below)

*Fourth operation—Ablation of left eye fields*—Some hours after the previous operation the left frontal eye fields (area 8) were ablated by Dr Margaret Kennard who will describe the results in another connection

#### SUMMARY OF FINDINGS

1 Stimulation of the fields in the *right* cerebral cortex resulted in conjugate deviation of eyes to the opposite side \* The globe moved slightly past the midline toward the left while the right upper eyelid retracted

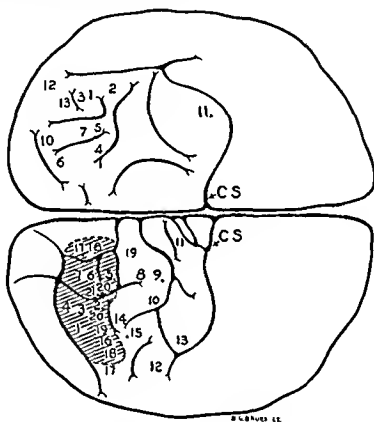


FIG 4 Diagram of the hemispheres showing the principal points stimulated in outlining the eye fields For key to points see *Appendix*

2. Stimulation of eye field in the left cerebral hemisphere yielded conjugate movement of eyes to the right (Fig 4) The right upper eyelid became slightly elevated with these ocular movements

3 Section of the reunited oculomotor nerve 110 days after it was first cut resulted in the reappearance of ophthalmoplegia (Fig 3) and external strabismus, there was at first no dilatation of the pupil, since the pupil had for another purpose been constricted by instillation of eserine 5 hours prior to the resection of the III<sup>d</sup> nerve After the effects of eserine had worn off the dilatation of the pupil became evident

4 Stimulation of the eye fields following the second cutting of the right oculomotor nerve failed to elicit movement in the right superior eyelid or right internal rectus muscle When the right cortical eye field was stimulated to cause the eyes to move conjugately to the left, the right globe moved, but only to the midline (Fig 4) This movement was interpreted as due to relaxation of the right external rectus muscle (Sherrington, 1893, 1899)

\* Repeated stimulation causing the eyes to move to the left was followed by conjugate deviation of eyes to the right when at rest This was interpreted as relaxation in the fatigued group of muscles and thus secondary deviation of the eyes by the non fatigued group of muscles

*Postoperative notes (Fourth operation).*—When the chimpanzee recovered from the anesthetic one hour after resection of its III<sup>d</sup> nerve, in addition to the right oculomotor ophthalmoplegia, the left eye was found deviated to the left. Rarely did the left eye move beyond the midline to the right. This restriction of eye movement to the right seemed to be part of supranuclear conjugate paralysis as a result of extirpation of the left eye field (Kennard and Ectors, 1938). The head was turned persistently to the left and when the animal walked, it invariably turned to the left, the eyes moving first, then the head, then the neck and upper trunk, the rotation movements occurring in spiral fashion. The fields of vision were normal; the animal reacted to confrontation tests in the right as well as the left fields of vision.

Four hours after the operation, the head and eye deviation toward the left became less prominent, although the animal still tended to rotate toward the left in its movements. Six hours after operation the head was practically in the midline, the left eye was slightly deviated to the left and the animal when attempting to move, did so to the left. When the left eye moved to the left, the right eyeball moved from the outer canthus to the left, but only to the midline. Eighteen hours after operation the general condition was the same. When in motion, the chimpanzee circled toward the left.

After 24 hours the right and left cerebral cortices were reexposed and the eye fields were again stimulated. No responses were obtained on stimulating the right eye field at this time. Subsequent stimulation, however, caused the left eye to move out to the left, while the right eye moved toward the midline.

*Fifth operation—Ablation of right occipital lobe.*—The right occipital lobe was then ablated on May 27, 1937. Following this procedure, both eyes were found conjugately deviated to the right. So long as the chimpanzee was under deep anesthesia, the eyes remained deviated to the right. When the anesthesia was light, the eyes returned to the midline position. Stimulation of the cerebellar hemispheres produced no responses either in the eyes or in any of the extremities. The animal was then sacrificed (May 27) under deep anesthesia for histological study.

### III. DISCUSSION

The muscles supplied by the oculomotor nerve are the superior, inferior, and internal recti, levator palpebrarum, inferior oblique, pupillary constrictor sphincter and ciliary muscles. When this nerve is electrically stimulated, all structures innervated react. The resultant visible effects are retraction of the superior eyelid by the levator palpebrarum muscle, internal rotation of the globe by the internal rectus muscle, and constriction of the pupil by the sphincter constrictor fibers.\* Vertical movements of the globe are not apparent because the action of the inferior rectus is antagonistic to that of the superior rectus and inferior oblique muscles. When these contract simultaneously there is little resultant motion. Furthermore, the action of the internal rectus is enhanced by the fact that the antagonistic muscle, the external rectus, is relaxed. With such apparently reenforced action, the eyeball is pulled on a horizontal plane nasally rather than in any other direction. On electrical stimulation of the normal oculomotor nerve, discrete action in individual muscles could not be obtained.

After section and regeneration of the oculomotor nerve in the chimpanzee, a similar picture was obtained. It appeared that all muscles, never one, contracted. Whenever the inferior or internal rectus muscle was stimulated to contract, there occurred retraction of the superior eyelid and inward move-

\* These observations were made in monkeys in which the normal and regenerated oculomotor nerves were electrically stimulated (M.B.B.).

ment of the globe. Vertical rotation of the eyeball was not observed. Identical conditions have been described in the human (Bender, 1936). Pupillary constriction as noted on electric stimulation of the normal oculomotor nerve was conspicuously absent. Apparently regeneration to the pupillary sphincter muscle had not taken place. However, some evidence for recovery in this structure may be found in the gradual lessening of the pupillary dilatation; that is, return of tone in pupillary constrictor muscle. Active contraction of the pupil in association with an impulse to the inferior rectus muscle in a man who showed evidence of oculomotor nerve regeneration has been described (Bender and Alpert, 1937). The constriction of the pupil in this case was part of a contraction of all structures innervated by the oculomotor nerve.

With regard to this apparent lack of pupillary function in the chimpanzee, it must be remembered that when the oculomotor nerve is cut intracranially, the fibers degenerate only as far as the ciliary ganglion. When regeneration occurs, the fibers reunite with cells in the ciliary ganglion and not the m. sphincter pupillae directly. The nerve endings in the ciliary muscle did not degenerate. These factors may play a rôle in the delayed recovery of function of the pupillary constrictor fibers. Perhaps with time, pupillary movements might have been detected.

The phenomenon of simultaneous contraction in muscles supplied by a regenerated nerve with loss of individual action has an anatomical basis. In numerous experimental studies, morphological evidence of nerve regeneration has been found as early as one day after the nerve had been cut. Axons from the central stump grow out into the exudate and break up into many branches, making, as is well known, a compressed regenerating mass of fiber. The axons in the peripheral stump do not occupy the nerve sheaths corresponding to those of the central stump. Furthermore, intermingled with the axis cylinders of the medullated nerve fibers are those of the non-medullated type.

With such structural alterations a stimulus conducted in the central stump along a set of fibers which normally supplies one group of muscles is shunted at the scar by way of the regenerated axis cylinders to fibers which carry impulses to other groups of muscles. Thus contraction of individual muscles would be impossible. The degree of contraction in each of the recovered muscles would depend on the number and variety of regenerated nerve fibers it received. Some muscles, like the levator palpebrarum in the chimpanzee described, might be reinnervated chiefly by fibers of the inferior rectus and internal rectus, and but little by branches from other nerves in the central stump. Such regeneration would explain why the upper lid retracted on downward and nasal gaze but not on upward gaze.

#### SUMMARY

1. Observations of functional recovery following section of the oculomotor nerve of a chimpanzee are recorded.

2. Inward or attempted downward movement of the affected eye caused

# ELECTRICAL EXCITABILITY OF THE MOTOR FACE AREA: A COMPARATIVE STUDY IN PRIMATES\*

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## I. INTRODUCTION

ANALYSIS of functional localization in the cerebral cortex has led to a progressively closer correlation with structural characteristics. The important pioneer studies of the Vogts<sup>15</sup> were the first on the cytoarchitecture of functionally discrete cortical areas. Investigations of the effects of ablation of the arm and leg areas in monkeys and anthropoids have recently been carried out by Fulton and his collaborators<sup>7</sup> but the areas controlling movements of the face, head and neck have been little studied and there remain many points of uncertainty. In the present study the effects of localized cortical ablation of the face area have been observed as well as the characteristics of its excitability. In order to correlate electrical responsiveness with structural detail, histological examination by serial section has been made of the experimental brains. The results will be presented in two papers, the first dealing with the excitability and the second with the effects of ablation of the "face area" of the cerebral cortex and its component parts.

### *Historical review*

The responses of the facial musculature to cortical excitation were studied in detail by Beevor and Horsley.<sup>1,2</sup> From the inferior part of the precentral convolution they obtained a great variety of facial and lingual movements, which they described minutely. Movements of the face were most frequently observed when the upper portion of this cortex was stimulated, and lingual movements result from stimulation in the extreme inferior portion of the precentral convolution. Laryngeal movements were described about the same time by Semon and Horsley.<sup>12</sup> In the latter part of the 19th century Spencer<sup>14</sup> initiated the study of respiratory changes. Although the subject was discussed by others<sup>9</sup> the next important advance was made by Cécile and Oskar Vogt<sup>15</sup> in 1919, who described in detail the reactions to cortical stimulation of the motor face area and correlated them with the cytoarchitectural structure of the cortex. They found that excitation of the gigantopyramidal cell area (area 4) gave rise to discrete responses of the cephalic musculature with a low threshold of stimulation. From the area just rostral to this, area 6aa, with somewhat stronger stimuli, more complicated movements arose. Just inferior to this area, about the sulcus subcentralis anterior, was a zone (area 6ba) from which rhythmical masticatory movements of the tongue, jaw and pharyngeal muscles were obtained. Stimulation slightly anteriorly (area 6bβ) produced alterations in respiratory rate and rhythm. In the intact cortex rhythmical movements of the tongue and jaw were seen with stronger stimulation of area 3a (lower part). The experimental findings of the Vogts have been confirmed in man by Foerster<sup>6</sup> and Cushing,<sup>3</sup> but histological correlations could not be made with clinical studies. The respiratory changes evoked by cortical stimulation have

\* This work was aided by grants from the Research Funds, Yale University School of Medicine.

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been studied recently by Smith,<sup>13</sup> and by Bucy and Case.<sup>4</sup> These authors report inhibition of respiration by stimulating a small area in the oral part of the human precentral gyrus.

### *Methods and technique*

**Animals.** The responses to electrical cortical excitation have been studied in 33 monkeys (*Macaca mulatta*) of which 3 were in such poor condition that no results were possible, 4 baboons (*Papio papio*), 4 chimpanzees (*Pan satyrus*), 1 mangabey (*Cercocebus aethiops*), and 1 spider monkey (*Ateles ater*). The cortex in the face region was intact in 29 animals; 11 had one or more cerebral ablations of the motor or premotor face area at least one month previously. The latter animals make it possible to demonstrate the effect of excitation of the various cytoarchitectural areas in the absence of adjacent regions. In some animals superficial cortical incisions were made at the time of stimulation, but this, as commonly occurs, often led to dubious results because of "shock" and depression of cortical activity.

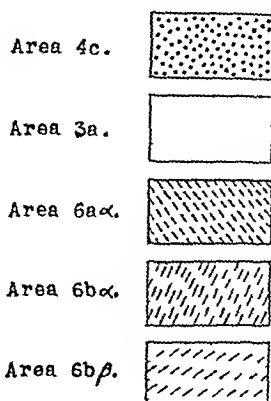
**Stimuli.** The cortex was excited by several methods. In the early experiments (17 occasions) the Harvard inductorium was used. Later (12 cases) stimulation was obtained by repeated condensor discharges through a thyatron tube and loosely coupled step up transformer, while still later a sixty-cycle A.C. sine wave (13 cases) current was employed. Galvanic stimulation was used in 3 experiments, the source being one or two 6-volt storage batteries in series. In many experiments the several forms of stimulation were compared. Bipolar metal electrodes, separated 2 mm., were used. As a routine procedure the cortex was stimulated for 5 seconds with 1 minute between tests.

**Respiratory tracings.** Respiration was recorded on smoked paper, by attaching a recording tambour to one arm of a tracheal cannula or to a partially inflated blood pressure cuff fastened around the thorax.

**Histological control.** At the time of stimulation representative points were marked on the cerebral cortex with india ink. The brain was later fixed in formalin or 95 per cent alcohol and the cortical markings of the inferior frontal region indicated by ink lines traced upon cellophane. The inferior frontal region with a generous amount of adjacent cortex on all borders was embedded in celloidin and sectioned serially at 20 to 25 micra, every 25th section being stained with toluidin blue or thionin and mounted. These sections were studied microscopically, and every 50th drawn at a magnification of 2, the cytoarchitectural areas being marked upon the drawing. Every operated cortex and a number of normal ones were so treated. In all, the brains of 22 animals, including chimpanzees, baboons and macaques, have been studied in this manner, representing more than 40 hemispheres; in 2 baboons and 2 macaques the cortex of the face area was sectioned serially and stained for myelin according to the Weigert-Pal technique.

**Terminology.** The terminology used in the description of the cortical areas follows that of the Vogts in their description of the cortex of *cercopithecus*. The term motor cortex or motor area will be used as synonymous with area 4 and premotor interchangeably with area 6 (Fig. 1).

The following abbreviations and symbols have been used:



C. S.	sulcus centralis
I. P.	sulcus precentralis inferior
S. A.	sulcus subcentralis anterior
S. S.	sulcus Sylvii

## II. THE MORPHOLOGY, ANATOMICAL RELATIONS AND ARCHITECTONICS OF THE FACE MOTOR AREA

The configuration of the inferior portion of the precentral convolution of the macaque and baboon is usually constant. Near its inferior extremity, the central sulcus swings posteriorly to terminate half a centimeter above the sylvian fissure. Between the central sulcus and the vertical limb of the inferior precentral sulcus (frequently termed the arcuate sulcus) lies a triangular area bounded inferiorly by the sylvian fissure. In its middle is a small dimple, a rudimentary sulcus, termed the *sulcus subcentralis anterior* (Fig. 1). A fairly constant feature of the macaque and baboon cortex is a small vein passing from the horizontal limb of the precentral sulcus inferiorly and posteriorly to the central sulcus joining the latter approximately a centimeter from its lower extremity. This vein is an important landmark, for excitation of a point in the superior angle between it and the central sulcus almost always gives rise to flexion of the contralateral thumb, and stimulation of a point in its inferior angle produces retraction of the contralateral angle of the mouth. The face area then consists of a triangular area between the inferior limb of the precentral sulcus anteriorly, the above mentioned vein and the central sulcus posteriorly, and the sylvian fissure inferiorly.

*Anatomical relationships.* The afferent connections of the cortex of the face area are of two types, one subcortical and the other cortical. The main subcortical projection arises from the medial portion of the anterior half of the lateral nuclear mass of the thalamus.<sup>16</sup> This projection terminates almost entirely in area 4, only a few fibers passing to area 6. The significance of this connection lies in the fact that the afferent connections of this part of the

thalamus are from the dentate nucleus of the cerebellum. It is probably through this mechanism that the cerebellum maintains a coordinating influence upon the volitional motor activity of the cerebral cortex. Transcortical connections are numerous from both the postcentral convolution and the prefrontal areas (Mettler<sup>10,11</sup>). The efferent projections from this area are not so well known. Mettler<sup>10</sup> and Levin<sup>8</sup> have both studied Marchi degenerations from lesions of this area in the monkey. We have also examined three preparations serially sectioned after being treated according to Marchi technique. The lesions were confined respectively to the motor and premotor areas, the premotor area, and the motor area. In general, a projection system passes

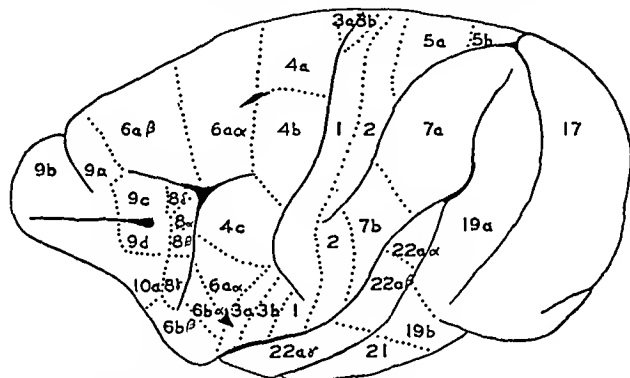


FIG. 1. Cytoarchitectural divisions of the cerebral cortex of the cercopithecine monkey according to the Vogts' investigation.

from both the motor and premotor areas, through the knee of the internal capsule and the medial third of the peduncle to the pons. In its course fibers are given to the thalamus, substantia nigra and subthalamic regions. In the pons numerous corticopontine fibers break up in the dorsal pontine nuclei. Corticobulbar fibers leave the main group of descending fibers in the cerebral peduncle to lie at the ventral border of the tegmentum adjacent to the medial lemniscus. From there fibers pass into the tegmentum and reticular substance, but no bundles reach any of the cranial nerve nuclei. Presumably an intercalated neuron is present or these fibers arborize about the dendrites of the cells of the cranial nerve nuclei.

*Cytoarchitectural pattern.* Within this area are several distinct cytoarchitectural and myeloarchitectural divisions. Although the general architectural characteristics of this part of the precentral convolution conform to those of the superior portion, it has certain unique features. The motor (area 4) and premotor (area 6) regions are readily distinguished and the latter may be sub-



divided into three distinct parts. In the posteroinferior corner of the face motor area the sensory cortex (area 3) extends anterior to the central sulcus.

*Area 4.* This portion of the face region presents the general characteristics of the gigantopyramidal area, *i.e.*, thick, agranular cortex with comparatively large, sharply staining Betz cells in the fifth layer. These cells do not reach the enormous size of those in the leg and arm areas, rarely attaining a diameter of 50 micra nor are they found in the same profusion as in the latter areas. They are not uniformly dispersed, but occur more frequently along the upper part of the central sulcus and are sparsely scattered anteriorly (see Fig. 2A). Superiorly the area extends from the central almost to the inferior precentral sulcus but tapers inferiorly to the anterior lip of the central sulcus.

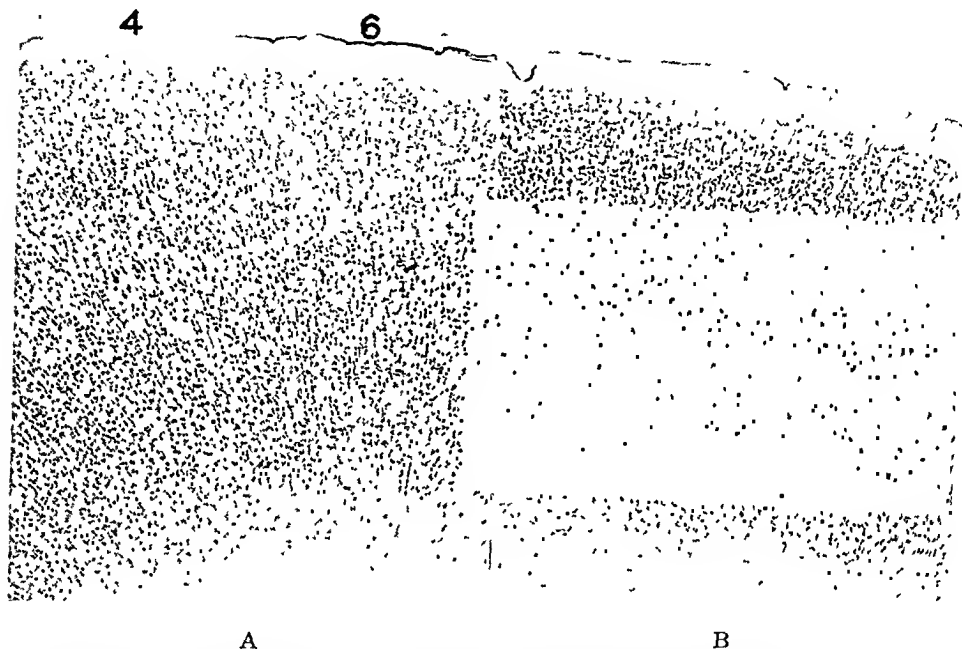


FIG. 2. Photomicrographs to show the cytoarchitectural appearance of the cerebral cortex of the face motor area. A. Areas 4c and 6aa. B. Area 6ba.

*Area 6.* Lying anterior to the gigantopyramidal area and extending to the depth of the inferior precentral sulcus is a zone of agranular cortex, area 6aa, presenting the same characteristics as that bordering the gigantopyramidal area in the arm and leg areas. It is, in fact, in direct continuity and indistinguishable from that portion (see Fig. 2A). Immediately inferior to this area, with a fairly abrupt transition, is a distinct type of agranular frontal cortex characterized by a heaping up of the medium sized pyramidal cells just below the fourth layer, giving the appearance of a dense granular fourth layer (see Fig. 2B.) This area 6ba is quite characteristic and readily distinguished. It extends as a strip along the inferior margins of areas 4c and 6aa from the anterior subcentral sulcus to the lower portion of the inferior precentral sulcus. Anterior and inferior to this area, the cortex of area 6ba is slightly modified, the heaping of the fourth layer becoming less prominent, and the cells of the fifth layer slightly smaller. This portion is area 6bβ of the Vogts. It has a faint but definite granular layer, which traced anteriorly becomes more pronounced as this type of cortex merges into area 10.

The posterior margins of these latter two types of area 6 cortex along the anterior subcentral sulcus sharply give way to the cortex of area 3a. This sensory or granular cortex extends anteriorly from the tip of the central sulcus to the anterior subcentral sulcus

and inferiorly almost to the sylvian fissure. It is characterized by its thinness, and the presence of occasional large cells in the 3rd and 5th layers, which distinguishes it from the cortex of area 3b and 1.

*Myeloarchitectural pattern.* The myeloarchitecture of the divisions of the face area is not quite so distinctive as the cytoarchitecture. In myelin stained preparations area 3 is characterized by its thinness, and the presence of a dense transverse layer of myelin fibers in the fourth layer. In the motor or gigantopyramidal area, the increased thickness of the cortex is more apparent and the transverse bands less prominent. In area 6 the latter is still less pronounced.

### III. THE RESULTS OF ELECTRICAL STIMULATION OF THE FACE AREA

Electrical excitation of each cytoarchitectural area causes a more or less characteristic response which may be modified by an interplay between the constituent parts of the motor areas. It is therefore necessary to consider the response of the individual parts of the face area to electrical stimulation both in the intact normal cortex and in the isolated cytoarchitectural area, for the latter response while not physiological is essential for an analysis of the part played by each cortical area in a movement.

#### *The principal areas*

**Area 4.** The characteristic response from electrical excitation of area 4 of the face region is a brief contraction of an individual muscle of the contralateral face or a smooth sustained contraction of a group of muscles (see Fig. 3). The fine twitch of a small group of muscle fibers is best elicited by galvanic excitation of the motor cortex; sustained responses may be obtained by faradic or sinusoidal stimulation. The threshold of excitation of the cortex within the area is not uniform; usually from a small area along the anterior lip of the central sulcus in the upper part of the face area, a minimal stimulus, insufficient to elicit a response from any other part of the face area, will give rise to retraction of the contralateral angle of the mouth. With the same stimulus, this response may be carried to any part of the motor face area by facilitation, i.e., successive stimulation of adjacent points. It cannot be carried with this minimal stimulus into the suprajacent arm area or into area 6, although a somewhat stronger strength of excitation will allow this response to be carried to area 6 of the face region. Slightly stronger stimuli will give rise to other primary responses from area 4, in general the response is in the facial musculature when the upper part of the cortical face area is stimulated, and in the tongue when area 4 near the tip of the central sulcus is excited. The usual response of the tongue is deviation and rotation to either side, but many variations may be present. Movements of the soft palate may result from stimulation of this lower part, but vocal cord movements have not been observed. With slightly supraliminal stimuli, parts of area 4 may give a response while intermediate points are unresponsive. This phenomenon is probably related to the scattered collections of Betz cells, especially since such cells are most numerous in the superior portion of area 4 (face part) lying along the anterior margin of the central sulcus, from which area a response is produced by minimal stimuli.

These characteristic responses from area 4 are present even after area 6 has been removed. In fact, if all but a few Betz cells are ablated, a typical response may still be obtained from these remaining cells. It therefore follows that the response from area 4 is independent of any adjacent cortical areas. However, a certain interrelationship of areas 4 and 6 may be shown with slightly stronger stimuli. If the point with minimal threshold in area 4 is

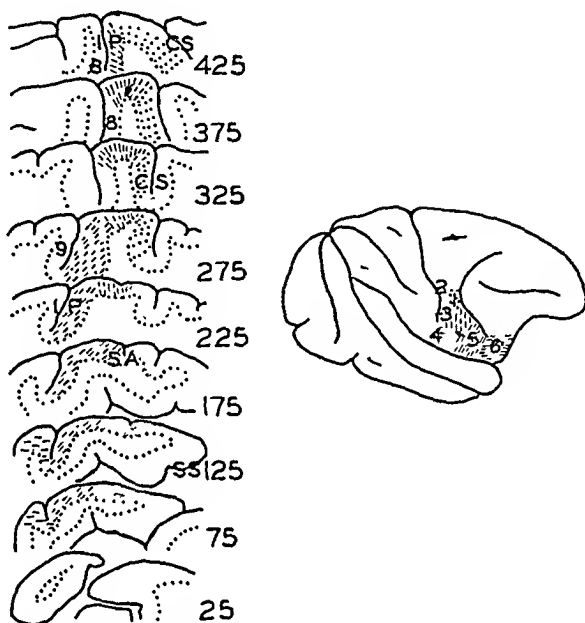


FIG. 3. (Area 6, 59) Sketch of the right cerebral hemisphere to show the cytoarchitectural areas of the face motor region in a macaque monkey, and representative sections of the same cortex to show the precise limits of the different areas. The following responses were elicited by electrical excitation with a sine wave 60-cycle alternating current:

- Point 1. (2 volts) Retraction of the left angle of the mouth.
- Point 2. (2 volts) Elevation of the left shoulder.
- Point 3. (2 volts) Protrusion and slight deviation of the tongue to the left side.
- Point 4. (2 volts) No response.
- Point 5. (2 volts) Rhythmical opening and closing of the jaw with backward and forward movement of the tongue.
- Point 6. (5 volts) Arrest of respiration (see Fig. 6).

stimulated with a liminal stimulus, the response may be obtained from adjacent parts of area 4 by facilitation, but cannot be carried to any adjacent areas. With slightly stronger stimuli it is possible to facilitate the response into area 6a and carry it to the boundaries of this area. With somewhat stronger excitation the response may be carried into areas 6b, 3 and 1 (Fig. 5). It cannot be carried into the arm region, for as soon as the boundary between the face and arm region is passed the face response is lost and a finger movement appears.

**Area 6** In general the threshold of area 6 is definitely higher than that of area 4. Responses from area 6, contrary to those from area 4, cannot be carried by facilitation, because stimulation of an adjacent cortical point gives rise to a new response

**Area 6aa.** Each of the three cytoarchitectural subdivisions of area 6 have more or less specific responses to electrical excitation. Excitation of area

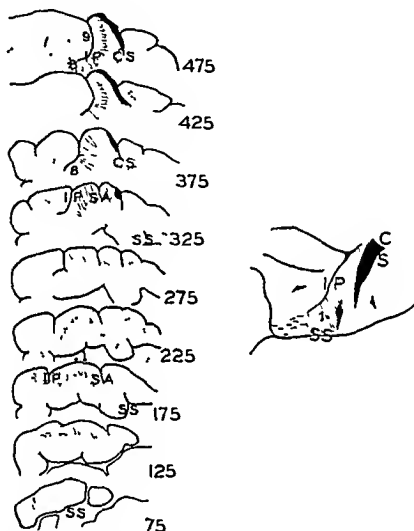


FIG 4 (Area 6, 68) The cytoarchitectural areas of the motor face area of the baboon (*Papio papio*). In this animal area 4 was completely removed 5 months previously (the ablated area is in black). Excitation of the entire remaining face region caused no motor response except from the area surrounding point 1, from which rhythmical chewing movements of the jaws and tongue were elicited. The point was marked with india ink, and its precise position as revealed by serial sections of the cortex is shown in section 175.

6aa gives rise to rather complex movements of groups of facial muscles, but never to twitches of individual ones. Entire ablation of area 4 largely destroys the responsiveness of area 6aa (Fig. 4). Strong stimuli cause, after a latent period, feeble rhythmical masticatory movements from its lower part if 6ba is intact, but a superficial incision between areas 4 and 6 (made in area 6, 1-2 mm from the border of area 4, in 5 experiments) does no more than temporarily impair the response. After 15-20 minutes the shock passes off and the cortex responds as formerly to the same strength of stimulus. It is there-

fore probable that the responses seen from area 6a are the result of short subcortical U fibers between it and area 4.

*Area 6ba.* Excitation of area 6ba with stimuli slightly suprathreshold for area 4 produces a characteristic response consisting of rhythmical opening and closing of the mouth, with or without protrusion and retraction of the tongue. This response may be maintained for a long period of time, but cannot be carried by facilitation to adjoining parts of the cerebral cortex. It is quite independent of the adjacent cortex of area 4, and persists in the

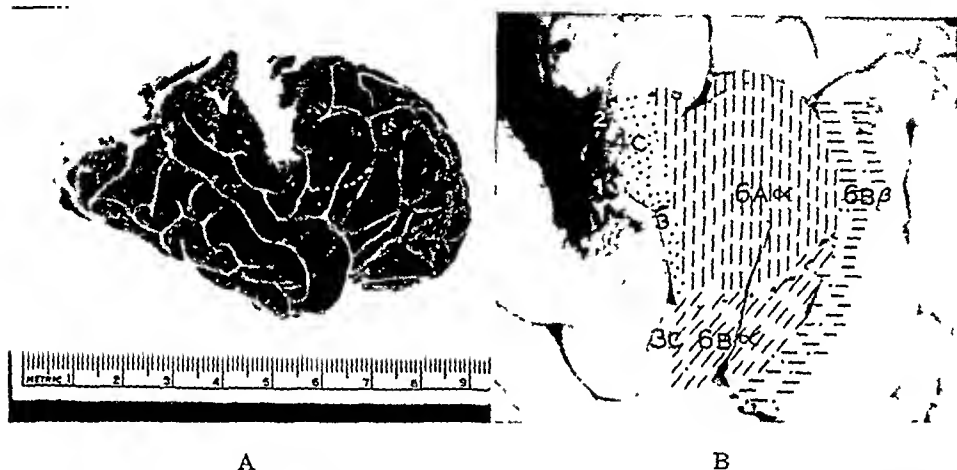


FIG. 5. (Chimp. S.) A. normal size. B. Enlargement of the cortical face area to show the cytoarchitectural areas. Using  $10\frac{1}{2}$  volt galvanic stimuli the following responses were obtained:

Point 3. Twitching in the contralateral side of the tip of the tongue.

Point 2. Twitching in the contralateral cheek muscles.

No responses could be obtained outside area 4 with this form of excitation. Stimulation of point 3 with  $1\frac{1}{2}$  volt sine wave 60-cycle current produced deviation of the tongue to the left side. This response could be produced from any point in area 4 by facilitation but as a primary response from point 3 only. Using a stimulus of 2.5 volts it could be facilitated to any point in areas 4c and 6a but not to area 6ba or 6bβ (within the area outlines in A). Primary responses elicited by a stimulus of 2.5 volts were as follows:

Point 1. Extension of the left thumb.

Point 2. Retraction and elevation of the left upper lip.

Point 3. Deviation and protrusion of the tongue to the left side.

complete absence of area 4. Rhythmical movements of jaw, tongue and pharynx are readily elicited in the monkey and baboon but in the chimpanzee we were able to produce only rhythmical movements of the tongue. Beevor and Horsley<sup>1</sup> were also unable to elicit masticatory movements in the orang. In the intact cortex these rhythmical movements may be associated with slow complex movements of the tongue before the onset of the rhythmical component (see Figs. 3 and 4).

*Area 6bβ.* Excitation of area 6bβ in five of 15 experiments, 10 monkeys, 2 baboons and 3 chimpanzees, in which respiration was recorded produced an

alteration of the respiratory rate and depth (Fig. 3). Respiration is usually completely arrested in expiration for 10-15 seconds, although after 9-10 seconds a respiratory effort may break through (Fig. 6), and occasionally only a diminution of excursion is present. Although respiration was arrested

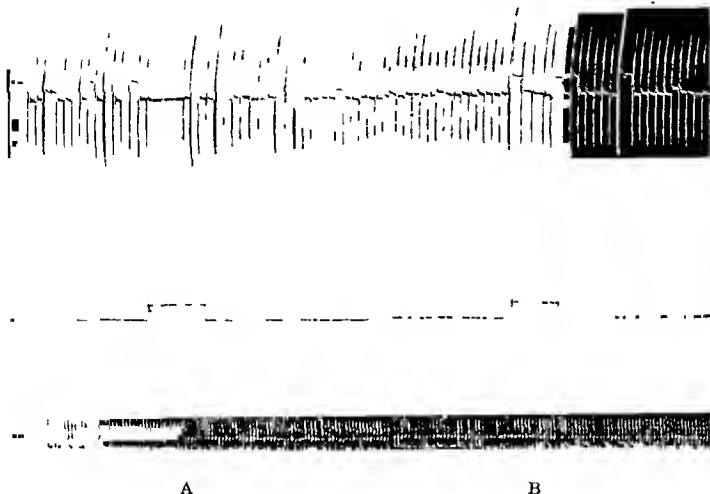


FIG. 6. (Area 6, 59) Respiratory record showing, A. complete temporary arrest of respiration following stimulation of area 6h $\beta$  (point 1, Fig. 3). B. slowing of the respiratory rate from stimulation slightly anterior to point 1 of the previous tracing at the junction of areas 6h $\beta$  and 6ba. (The strength of excitation was 5 volts using a 60-cycle sine wave stimulus; respiratory record is a tachygram recorded from the tracheal canula; time is shown in seconds at the base of the record.)

in expiration in all our experiments other investigators have described its cessation in forced inspiration or expiration and in normal inspiration or expiration.<sup>13,4</sup> The response is quite independent of the motor area or other portions of the premotor cortex. The best results were obtained from the monkey, but were observed in the baboon and chimpanzee.

**Area 3a.** Area 3 which extends anterior to the central sulcus is inexcitable in the absence of area 4. In the intact cortex, however, strong stimuli produce simple movements of the facial musculature or of the tongue. Similar movements have been observed from excitation of the postcentral convolution (area 2). Incision of the cortex superficially does not abolish these responses

but deep incision does. It seems probable, therefore, that such responses are the result of subcortical connections to area 4, although spread of current is not excluded.

### *Ipsilateral cortical representation*

It is difficult to produce isolated movements of the mm. orbicularis oculi or frontalis from cortical stimulation, but in 2 experiments we have seen them; usually the response is bilateral, occasionally only contralateral. In only one instance have we seen ipsilateral contraction of the lower facial musculature as the result of cortical excitation. In one experiment excitation of area 8 elicited a protraction of the contralateral pinna.

The tongue, however, has extensive bilateral representation in the cerebral cortex. Section of one hypoglossal nerve (6 experiments) causes only a moderate poverty of lingual movements. When the cerebral cortex contralateral to the section is stimulated, practically every movement of the tongue, deviation to both sides, rotation, protrusion, and rhythmical movements, may be elicited. The range of movement especially to the contralateral side is impaired and the denervated half of the tongue is only passively moved, but the response from ipsilateral cortical stimulation is still so rich that casual observers have suggested that the nerve section was incomplete. Subsequent section, however, of the second hypoglossal completely abolishes all lingual response from cortical stimulation. The ipsilateral responses may be just as readily obtained from area 4c as from areas 6a $\alpha$  and 6b $\alpha$ .

### *Other effects from cortical stimulation*

Other responses to excitation of the cortical face motor area were carefully observed. We have never seen pupillary alteration or eye movements although these often result from stimulation just anterior to the inferior precentral sulcus in area 8.

*Inhibition.* On numerous occasions we have attempted unsuccessfully to inhibit the artificially induced response by excitation of the opposite cerebral cortex. The usual effect of such simultaneous bilateral stimulation is to complicate the movement with a second component. This is particularly evident with comparable points producing lingual movements. In one experiment we have been able repeatedly to inhibit the rhythmical tongue movements elicited from area 6a $\alpha$  by stimulating the ipsilateral prefrontal granular cortex just anterior to the vertical limb of the inferior precentral sulcus (area 9c). We have also been able to inhibit the shivering under ether anesthesia by stimulation of areas 6b $\alpha$  and 6b $\beta$ .

In one case in which the lateral three-fourths of the cerebral peduncle was sectioned (histologically verified) no effects were obtained from stimulation of the face area. Excitation of area 8 produced good eye movements, and excitation of the upper part of area 6a $\alpha$  gave good ipsilateral responses in both the upper and lower extremities but none in the contralateral ones. Inhibition of voluntary movements and of ether postures also followed stimulation of the anterior part of this area.

*Vocal cord movements.* Vocalization as the result of cortical excitation was elicited in only one experiment. Movements of the vocal cords, however, frequently followed excitation of area 6ba in the macaque. These may occur in the absence of respiratory change and are bilateral.

*Salivation.* Frequently in the course of an experiment profuse salivation has been noted. Quantitative measurement proved impracticable and we can only say that excitation of the face motor area produces a definite augmentation of salivation, area 6 being somewhat more efficacious than area 4.

*Epilepsy.* Many investigators have noted that after prolonged excitation of the motor cortex, epileptic afterdischarge is frequent. We have had the privilege of stimulating several animals, previously used by Dr. R. U. Light in his studies on induced epilepsy. The tendency for an epileptic discharge to occur in these animals was so great that discrete responses could only be obtained by the use of liminal stimuli for 1-2 seconds; longer excitation even with these weak strengths produced an epileptic discharge.

#### IV. DISCUSSION

The present investigation largely confirms the original studies of Cécile and Oskar Vogt.<sup>15</sup> The division of the electrically excitable cortex, giving rise to cephalic movements, into areas having characteristic responses allows some insight into the function of the cerebral cortex. The proximity of the cortical areas concerned in the control of respiration, salivation and lingual, pharyngeal and laryngeal movements is evidence of nature's economy. Through simultaneous integration of these autonomic and somatic processes, which are physiologically intimately related, the cortex maintains a harmonious and well coordinated masticatory and deglutitory mechanism. Were not the respiratory movements so regulated, the danger of aspirating food would indeed make swallowing a hazardous process for the individual.

Such an analytic study indicates some of the possible roles which each part of the motor cortex may take in the normal performance of the brain. The functional divisions of the cortex are so interrelated that the activity of one modifies that of the other. This interplay is a fundamental process which has developed through phylogeny with the progressive differentiation of the cerebral cortex.

In rodents electrical stimulation of the cerebral cortex gives rise to rhythmic movements of the jaw and tongue but isolated single movements of the face or tongue are rarely seen. In these animals there is little cytoarchitectural differentiation between the component parts of the excitable cortex. In the carnivora, although cortical development has proceeded, individual muscle responses are still rare. It is not until the motor and premotor cortex become distinct, as in the lower primates, that discrete movements are readily elicited. With further differentiation, such as that present in the higher anthropoids and man, the generalized primitive response recedes and the discrete becomes more prominent. With this process of encephalization and cortical differentiation, a mechanism develops, as Foerster<sup>6</sup> and Fulton<sup>7</sup> have



emphasized, for the control and coordination of the activity of the differentiated motor responses. Subservient this function for the cephalic muscles is area 6aa (lower part). As has been shown, this area appears to operate through its adjacent cytoarchitectural zones, in the absence of which it is unresponsive. It is this portion of the face motor area which shows the greatest development in phylogeny (compare Figs. 3, 4 and 5) reaching its acme in man.

### SUMMARY

1. The cytoarchitectural characteristics of the face motor area of the macaque monkey, baboon and chimpanzee are discussed, and their response to electrical stimulation described.

2. From area 4, the characteristic response is a brief contraction of an individual muscle or group of muscles.

3. Stimulation of area 6aa gives rise to rather complex movements of groups of muscles; removal of the adjacent areas abolishes the response.

4. Rhythmical masticatory and deglutitory movements are obtained from stimulation of area 6ba; these responses are independent of the adjacent cytoarchitectural areas.

5. Stimulation of area 6b $\beta$  causes changes in the respiratory rhythm.

6. There is extensive bilateral representation of the tongue in the cerebral cortex.

7. Vocal cord movements and sialorrhoea have been obtained from stimulation of area 6.

8. The phylogenetic and physiological significance of these cortical responses is discussed.

It is a pleasure to acknowledge the generous suggestions and stimulating criticisms and encouragement given us by Professor John F. Fulton. We want also to thank Dr. D. Denny-Brown for his helpful advice during this research.

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*Addendum* Since this paper was submitted for publication Penfield and Boldrey have published the results of electrical stimulation of the cerebral cortex in a large number of human subjects Their studies do not, however, include any histological examinations of the stimulated areas (Reference Penfield, W and Boldrey, E Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation *Brain*, 1937, 60 389-443)

# FACILITATION OF REFLEX ACTION IN THE SPINAL CAT FOLLOWING ASPHYXIA OF THE CORD FROM CYANIDE AND INCREASED INTRA-SPINAL PRESSURE

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THE EFFECT of asphyxia on the spinal cord is sometimes lost sight of because of its more striking effects in relation to respiration. That asphyxia is a powerful stimulant to the spinal cord is well known to all who have worked with the spinal animal which exhibits violent convulsions as soon as artificial respiration is discontinued. The violence of this stimulation and its sudden onset have tended to distract attention from the fact that in asphyxia, as in strychnine poisoning, there is a stage, preceding the convulsions, of simple facilitation or spread of reflex action, no movement occurring unless a sense organ or nerve is stimulated. The injurious effect of asphyxia on reflex arc conduction rather than this early beneficial effect, has been emphasized, following Sherrington's (1906) original statement of the greater dependence of the reflex than of a nerve trunk on oxygen. But loss of reflex irritability occurs only during the later stages of extreme asphyxia, while more moderate asphyxia must be a much more frequent condition among animals as they meet the emergencies of life.

Moderate asphyxia of the spinal cord improves conduction and results in a spread of reflex activity. Sherrington (1909) in his early work on the spinal cat, found the scratch reflex more easily elicited under slight asphyxia. Graham-Brown (1909) confirmed this on the spinal guinea pig, and more recently Gesell and his co-workers (Gesell and Moyer, 1935; Winkler, 1929, 1930; Glazer, 1929, and Gay, 1930) have reported that in various types of asphyxia the reflex contraction of the dog's tibialis anticus was higher than with an adequate oxygen supply. These results were not uniform however and in many instances asphyxia acted deleteriously on the reflex instead of beneficially. The whole dog was used, under morphine-urethane anaesthesia and the irregular results are doubtless in part due to the effect of the anaesthetic. We think it likely that this anaesthesia, pushed to the surgical point, affected the spinal reflex threshold, for unpublished results show the delicate reflex preparation here used to be sensitive to much smaller morphine injections than required to act on the whole animal.

Our evidence favors the view that only synaptic junctions or reflex centers are involved when the reflex improves in slight asphyxia. (Gesell *et al.*, believed nerve and muscle were also affected.) Observations were made on the spinal cat without anaesthesia and using a minute muscle as a delicate

\* With the assistance of H. J. Frachtman in some experiments.

indicator of conduction in the reflex arc. Diminution of the oxygen supply to the cord, either by injection of cyanide or by increased intraspinal pressure, invariably caused a greater contraction due to an increase in the number of motor units involved, i.e., to a facilitation or improved synaptic conduction. Further, this degree of tissue asphyxia had no detectable effect on the motor nerve or the muscle and by inference none on the sensory nerve, so the improvement was entirely due to spread of conduction within the "motoneurone pool" of the particular muscle concerned. Finally, the increased discharge of motor neurones is not due to asphyxial stimulation of them, but only to a facilitation of conduction, since no contraction occurs except as a result of sensory stimulation.

### METHOD

The cat is etherized, carotids tied and brain destroyed, much as one would with a frog (See Porter and Allamon, 1936). The cord also is pithed down to the lower thoracic region. The right hind leg is denervated and the tenuissimus muscle of the left leg is prepared for registration.\* This muscle is so small in the cat that both as a nerve muscle and as a reflex preparation it can be made to show the contraction of individual motor units.† This has been described in a previous paper by Porter and Hart (1923) using optical recording. It has since been found possible to record the contraction of individual motor units more conveniently with a long straw on a smoked drum.

The muscle is exposed as previously described (Porter and Hart, 1923). A Harvard heart lever is cut to project 2 to 3 cm. on each side of the fulcrum and a light straw, 50 cm. long, is cemented on one arm for registration.‡ The other is bent at right angles to project into the wound and is fastened to the end of the muscle as it lies immersed in Ringer's solution. The movement of the muscle is magnified about 15 times. The weight of the straw is the only tension on the muscle.

With such a straw the friction of the pointer on the drum tends to prevent a proper return to the base line after a contraction. This difficulty is largely overcome by attaching a buzzer to the stand to which the lever clamp is fastened. The slight tremor of the straw reduces friction at the writing point and it returns properly to its original base line.§

The stimuli are break shocks from a large inductorium with the secondary at a considerable distance from the primary. The primary current is

\* In a series of 81 cats used for various purposes in the last three years tenuissimus has been absent in 2 cats, too small to use by our methods in 4 cats, and present and usable in all the others. Tenuissimus is also present in the dog.

† Small tail muscles also show very distinct step-like all-or-none increments and decrements of contraction both as nerve-muscle and as tonus contractions (Porter 1929), but, of course, are not suitable for a problem such as the one described in this paper, since they do not respond to electrical stimulation of sensory nerves, but only to such stimulation as causes change in tonus.

‡ These have been obtained from wholesale florists as part of wheat sheaves used for Thanksgiving decorations.

§ This device is not complicated with any special wiring. I do not know who first used it. The buzzer plugs into the regular 110-volt circuit. A

reduced to approximately 0.1 of an ampere and kept steady with resistance wire; and a uniform shock is obtained with a copper-mercury key.

The shocks are applied to the posterior tibial nerve through a special liquid electrode which maintains uniformity (Porter and Allamon, 1936). The wound for exposing the tenuissimus muscle is arranged as a shallow cup, and the muscle immersed in Ringer's solution. It is sometimes necessary to dust the wound edges with the difficultly soluble local anaesthetic, Anesthesin (Ethyl Aminobenzoate)\* to eliminate reflex tremors.

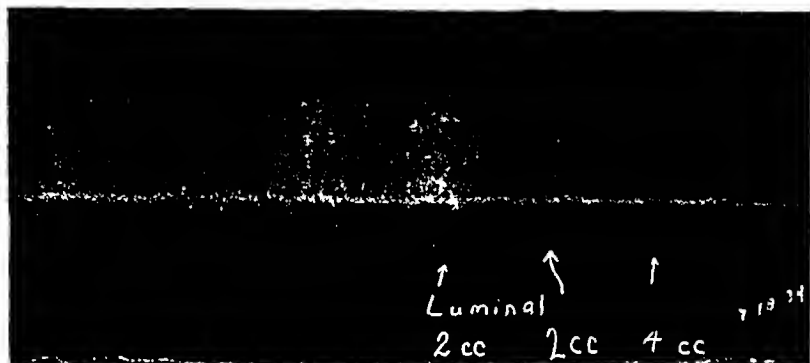


FIG. 1. Reflex contractions of tenuissimus muscle near the threshold. Contractions made up at first mainly of four motor units. (Some isolated contractions of a fifth.)

Successive intravenous injections of 1.5 per cent pheno-barbital (luminal) threw one motor unit after another out of action in all-or-none steps with complete extinction of the reflex after the third dose. Sensory stimuli (break shocks to posterior tibial nerve) unchanged during the record. Stimulation 45 per minute. Record natural size. Contraction magnified on drum about 25 times.

Since the tenuissimus originates from one of the vertebrae, it is impossible to prevent the movements of artificial respiration from causing slight undulations in the base line. To obviate an apparent variation in the height of the superposed contraction, the primary key is attached to the artificial respiration machine in such a way that a break shock is always given at the same point in the respiratory cycle. Reflex contractions, when recorded near the threshold, are seen to be of a few definite heights with no gradations between. As the stimuli are increased in strength the muscle contractions increase by definite steps (very clearly with optical recording, Porter and Hart, 1923). In Fig. 1 the initial height of reflex contraction, produced mostly by four motor units, was reduced in four steps by intravenous injections of luminal as indicated. Such steps in contraction height are almost certainly caused by single motor units, or neuro-muscular squads (Porter, 1929), passing into and out of action, and the record is thus an indication of the condition of the motoneurone pool. This is isotonic registration of the same phenomenon demonstrated by Liddell and Sherrington (1923) in their well

\* In perhaps one in 15 animals we have found it impossible to control these tremors.

known isometric studies of reflex contractions of larger muscles. It is not surprising that the activity of individual motor units should be detectable by our methods, since approximately 150 tenuissimus muscle fibers are innervated by one motor axon (Adrian, 1925) and there are probably only about 50 motor units in the entire muscle (Porter and Hart, 1923). Preliminary experiments indicate that the tibialis anticus shows the coarser features of the phenomena we shall describe, but the advantages of using the finer indicator—tenuissimus—are evident.

Asphyxia of the cord has been produced in two ways: (1) by the injection of sodium cyanide, and (2) by increased intraspinal pressure, following Cushing's technique for producing increased intracranial pressure (Cushing, 1901). These methods can easily be controlled and the latter has also the advantage of sharply localizing the asphyxia to the cord.

## RESULTS

### *Experiments with cyanide*

Cyanide acts by interfering with oxidizing enzymes so that the effect is that of oxygen want (Sollmann, 1936). Sensory stimulation was reduced until a few motor units, preferably only 2 or 3, contracted reflexly. 0.1 per cent sodium cyanide was rapidly injected into the external jugular vein, usually about 0.2 cc. corresponding to 0.1 mgm. per kgm. for the average cat. After a variable latent period (minimum 12 seconds), the height of contraction increases, often at first by only one or two steps, later by many. An example is shown in record A of Fig. 2. If a larger dose of cyanide is given, the condition passes into true convulsions which cannot be distinguished from those following strychnine injection. Cyanide is relatively rapidly altered in the body to the harmless thiocyanate (Sollmann, 1936) and within a short time after an injection, the contractions return to their original height. (Record B of Fig. 2.) We have usually allowed 10 or 15 minutes between injections, but a second can be effective 3 minutes after the first and possibly earlier.

We have made 41 injections on 13 cats. In no animal has cyanide failed to cause improvement in reflex contraction. A few separate injections have failed, but this has been attributed to the dose being too small or the injection too slow to reach effective concentration in the cord. Our minimal effective dosage was 0.05 mgm./kgm. Winder, Winder and Gesell (1933) obtained an increase in respiration from intravenous injection of cyanide in anaesthetized dogs after carotid sinus and vagus nerves had been put out of action with a minimal dose of 0.03 mgm./kgm. It is somewhat surprising, perhaps, that an effect on the spinal reflex can be demonstrated with a concentration of cyanide so close to that affecting the respiratory center.

### *Experiments with increased intraspinal pressure*

Cushing (1901) showed that increased intracranial pressure caused the blood vessels in the brain to diminish in size, sometimes to the point of

invisibility, with resultant symptoms of brain asphyxia. We have modified Cushing's original method to limit sharply the asphyxia to the cord. A plug of fine-grained sponge rubber is forced into the neural canal in the neck and a hypodermic needle connected with a pressure bottle of Ringer's solution is inserted either through the rubber plug, or more commonly between the last lumbar and first sacral vertebrae. The pressure bottle is then raised, usually



FIG. 2. Intravenous injections of cyanide in the spinal cat cause spread of reflex action within the reflex center, but not direct stimulation of motor neurones.

*Record A.* Reflex contractions of tenuissimus. Break shocks to posterior tibial nerve 45 per minute. Strength of shocks unchanged during the record. From 1 to 4 motor units (most frequently 2) in activity at first. At 6 an intravenous injection of cyanide, 0.4 mgm./kgm. At 6a a spread of reflex activity to an increased number of motor units. Between 7 and 8, and between 9 and 10, stimuli discontinued with resulting quiescence of the muscle, indicating that the cyanide has not been stimulating motoneurones directly, but facilitating reflex action. (The drop in base line following 6a is due to incipient convulsive movements in other parts of the body.)

*Record B.* To show the temporary effect of cyanide. Forty-five minutes later than Record A. The reflex has returned to the contraction of mostly 1 to 3 motor units, as at the beginning of the experiment.

rapidly, until an effect is produced on the height of the reflex contractions. Pressures used have varied from 70 to 150 cm. of water. Fig. 3 records the results of such a procedure with facilitated contractions appearing after a latent period of 24 seconds. The spread of reflex activity produced by increased intraspinal pressure is not a direct stimulation of motoneurones in the reflex center for contractions only follow reflex stimulation. This is shown in Fig. 4.

The question arises as to whether the improvement in the contraction height of the tenuissimus might not have been due to some direct effect of the two procedures on the nerve-muscle mechanism instead of to a reflex facilitation, as we have maintained. Winkler (1930) and Gay (1930) believed that injection of cyanide improved contraction by this means. Cyanide might conceivably do this, but it is not easy to see how an increased intraspinal pressure could improve nerve-muscle activity except by general changes in blood pressure. Actually, cyanide invariably lowered blood pressure (34 injections in 4 cats gave falls ranging from 4 mm. Hg.—initial pressure 35—to 22 mm. Hg.—initial pressure 57) and increased intraspinal pressure raised it (33

tests on 3 cats ranged from 2 mm. Hg. rise—initial pressure 74—to 76 mm. Hg.—initial pressure 74). One might imagine that the low pressure produced by cyanide was accompanied by vaso-dilatation in the muscle with improvement in contraction, or that the increased blood pressure following raised

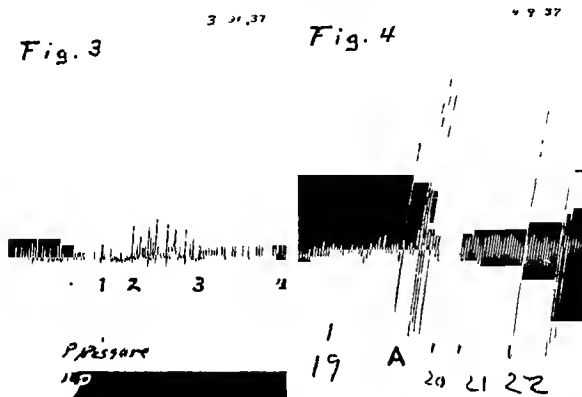


FIG. 3. Increased intraspinal pressure in the spinal cat results in increased height of reflex contraction of the tenuissimus muscle. Single shocks to posterior tibial nerve, unchanged in strength during the record. Record natural size. Magnification of muscle contraction about 15 times. Contractions at first involve 1 to 3 motor units, occasionally more. At 1 pressure bottle raised—height not noted—and bottle not lowered during the portion of record shown. At 2 the contractions involve additional motor units. Between 3 and 4 spread of reflex action indicated by greater regularity of second motor unit.

FIG. 4. The increased height of reflex contraction of tenuissimus muscle following increased intraspinal pressure is a facilitation, not a direct stimulation of motoneurons.

Contractions at first involve 1 or 2 motor units. At 19 pressure bottle raised (amount not noted) and intraspinal pressure increased. At A spread of reflex action to third motor unit (unusually high in this animal) and greater regularity of second. Between 20 and 21 the stimuli were discontinued, and reflex contractions ceased. Hence, intraspinal pressure was not stimulating motoneurons, but facilitating synaptic conduction. At 22 bottle lowered. Record natural size. Magnification of muscle contraction about 25 times. (Undulations in base line due to artificial respiration.)

intraspinal pressure led to a more rapid blood flow through the muscle, again with improvement in contraction.

The question of a possible direct effect of these procedures on nerve or muscle has been tested by cutting and stimulating the sciatic at the origin of the nerve to the tenuissimus after obtaining effects on the reflex. As seen in Fig. 5, and all experiments give like results, a dose of cyanide which greatly increased reflex contractions had no effect when repeated while the cut motor nerve was stimulated with supraminimal shocks.



A similar procedure has been employed to show that increased intraspinal pressure does not result in changes in the nerve-muscle preparation (Fig. 6). There is no improvement in contraction of the muscle when it is a part of a nerve-muscle preparation—at least in the sense of new motor units entering

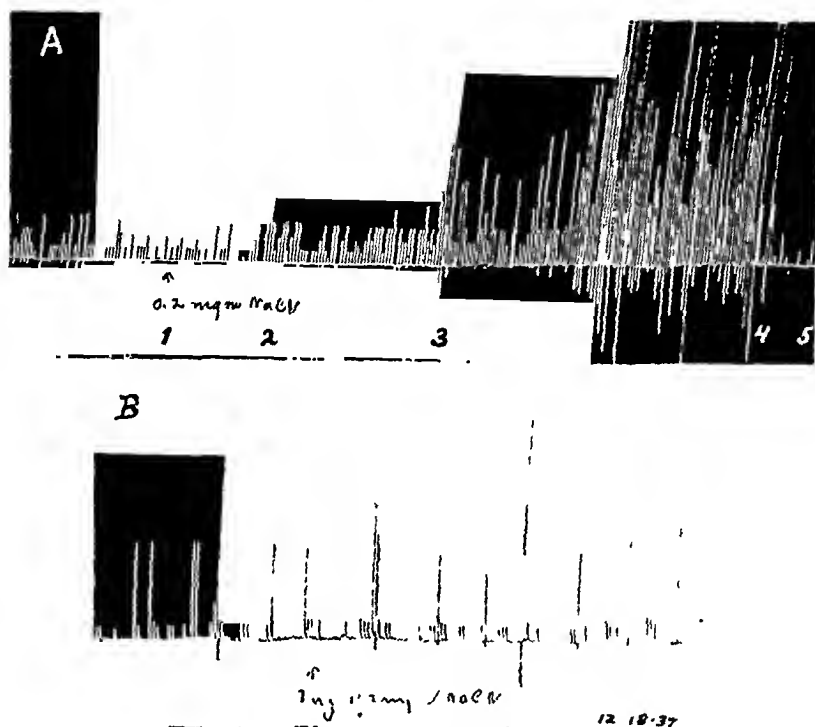


FIG. 5. Injections of cyanide affect only the reflex, not the nerve-muscle preparation.

*Record A.* Reflex contractions of tenuissimus from break shocks, 45 per minute, unchanged in strength during the record, applied to the posterior tibial nerve. Contractions at first mainly 1 motor unit high. At 1 an injection of sodium cyanide 0.05 mg./kgm. At 2 reflex activity spreads to include three motor units. Between 3 and 4 spread has become so extensive that it often is impossible to say how many motor units are involved. Between 4 and 5 the reflex contractions are involving again only 1 to 3 motor units, as at the beginning of the record.

*Record B.* The tenuissimus has been made a nerve-muscle preparation. An injection of cyanide equal in amount to that of record A produces no change in the number of motor units in activity. (Record B 2 hours 15 minutes later than record A.)

activity. In a few instances in nerve-muscle preparations the contraction of such motor units as were already in activity seemed improved following increased intraspinal pressure, never after injection of cyanide. This improvement is slight, occurs after the intraspinal pressure has been returned to normal, and is presumably referable to the increased blood pressure, but we have no data on that point.

In the present state of knowledge with regard to phenomena occurring within the spinal cord (cf. Forbes, 1936), it is, perhaps, futile to speculate on how asphyxia of the cord operates to cause spread of reflex action. It is not obvious how a neuro-humor within the center would be chemically

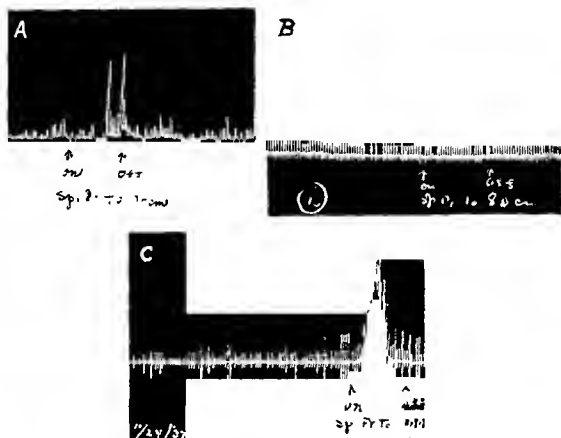


FIG. 6. Increased intraspinal pressure in the spinal cat improves reflex contractions only and has no effect on the nerve-muscle preparation.

*Record A.* Reflex contractions of tenuissimus with 1 to 3 motor units in activity at first. Between "on" and "off" the intraspinal pressure was increased, causing transient spread of activity to more motor units. On removal of increased intraspinal pressure reflex promptly returns to approximately the original height.

*Record B.* Tenuissimus now a nerve muscle preparation with only one motor unit in activity. Increased intraspinal pressure between the arrows had no effect on the height of contraction.

*Record C.* Same conditions as B, but the intraspinal pressure carried to a point such that convulsive movements elsewhere in the animal, indicating asphyxial effects on the cord, caused a rise in base line of the tenuissimus nerve-muscle preparation, but there is no change in height of tenuissimus contractions measured from this base line. Stimulation unchanged during each record. Magnification of contraction on drum about 15 times.

changed or cell surfaces at synaptic junctions be altered by oxygen lack. It is interesting, however, in this connection that Brinley (1928) finds that cyanide paralyzes ameba only when applied to the surface, not when injected into the protoplasm. But in any event, it seems clear that facilitation occurs in consequence of slight asphyxia of the cord, and it would appear that in formulating a theory of the nature of synaptic conduction this fact should not be lost sight of.

## SUMMARY AND CONCLUSIONS

- (1) A method is described by which the reflex contractions of the tenuissimus muscle in the spinal cat are used as an indicator of the state of activity of its reflex center.
- (2) This indicator is so delicate that the entrance into or exit from activity of individual motor units can be seen. Depression in the center is shown by a diminution of the number of motor units in activity; facilitation by an increase.
- (3) Slight asphyxia, caused by the intravenous injection of sodium cyanide, increases the number of motor units responding to the same strength of sensory stimulus as before.
- (4) The increased response is not a direct stimulation of motoneurons because no contraction occurs if sensory stimulation is discontinued during the period of increased contraction.
- (5) Asphyxia, produced by increased intraspinal pressure, acts similarly.
- (6) Both procedures cause changes in blood pressure in the spinal cat—cyanide a lowering and increased intraspinal pressure a rise.
- (7) Neither injections of cyanide nor increased intraspinal pressure cause new motor units to enter into the contraction when the tenuissimus is used as a nerve-muscle preparation.
- (8) It is concluded that the first effect of asphyxia, whether produced by the injection of cyanide or by increased intraspinal pressure, is the facilitation of reflex action, as shown by the spread of activity within the reflex center to motor units which were formerly not in activity.

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# THE DIRECT FUNCTIONAL INTERRELATION OF SENSORY CORTEX AND OPTIC THALAMUS\*†

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## INTRODUCTION

THE OPTIC thalamus is the last subcortical relay-station for all corticopetal sensory‡ systems. From its lateral, ventro-lateral and ventral nuclei originate the thalamo-cortical neurons to terminate in the sensory cortex. However, these nuclei are connected with the sensory cortex not only through these corticopetal fibers but also through innumerable corticofugal neurons, beginning in the sensory cortex and ending in these very same thalamic nuclei.<sup>8</sup> These two-way connections indicate a close functional interrelation between thalamus and sensory cortex. This interrelation was proposed first in 1911 by Head,<sup>6</sup> who, to explain the spontaneous pains and hypersensitivity of the skin frequently a component of the "thalamic syndrome," advanced the hypothesis that cortico-thalamic impulses inhibit thalamic activity. On the basis of his experiments with local strychninization of the monkey's cortex Dusser de Barenne in 1924<sup>1</sup> advanced two hypotheses, 1. that such strychninization "sets on fire" a much larger portion of the sensory cortex than the area strychninized, 2. that under these conditions the corresponding thalamic nucleus also is "fired" (l.c. p. 285 et seq.). The first of these hypotheses has been verified and amplified recently.<sup>4</sup> In this paper we bring the verification of the second hypothesis.

Inasmuch as the local strychninization§ anywhere in the sensory cortex produces "strychnine-spikes" in the electrocorticogram (ECG) of functionally related areas,<sup>4</sup> it was plausible to expect that the same local strychninization of this cortex might also "fire," i.e., produce strychnine-spikes in the electrothalamogram (ETG) of the related thalamic nucleus or nuclei. If this surmise proved to be correct, one would have here a physiological method for the investigation of the direct cortico-thalamic functional relations. To attack this problem it was necessary to know in which thalamic nucleus or nuclei the face, arms and legs are represented sensorially, i.e., to know the

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† The main result of this investigation was first presented as part of a symposium on "The Cerebral Cortex and Behavior" before the Section on Psychology of the Amer. Assoc. for the Advancement of Science at its Atlantic City Meeting, December 30, 1936. See *Amer. J. Physiol.*, 1937, 119: 263 and Communications XI. Congrès international de Psychologie, Paris, July 1937.

‡ In this paper the term "sensory" is applied to all nervous structures mediating sensation (exteroceptive, proprioceptive—perhaps interoceptive), other than vision, audition, olfaction and gustation.

§ With local strychninization is meant that the strychnine solution is applied to a few square millimeters of cortex.

functional localization in the thalamus of the monkey. This localization was established in 1934-1935 by intrathalamic strychninization, in combination with "clinical" observation of the ensuing sensory disturbances.<sup>3</sup>

Once this functional localization was known the experiments to be reported in this paper were, in principle, very simple: concentric needle-electrodes were introduced into a particular nucleus of the thalamus and the ETG recorded before and after the local strychninization of the various subdivisions of the sensory cortex.

These experiments have established the following, direct functional relation of the sensory cortex to the thalamus: each thalamic nucleus is "fired" by the local strychninization of that, and *only* that, subdivision of the sensory cortex which subserves sensation of the *same* part of the body.

A second group of experiments in which the ECG of the various subdivisions of the sensory cortex was taken before and after intrathalamic strychninization, has shown the following direct functional relation of the sensory nuclei of the thalamus to the sensory cortex: the injection of strychnine into any particular sensory thalamic nucleus "fires" that, and *only* that, subdivision of the sensory cortex which subserves sensation in the *same* part of the body.

#### METHOD

All experiments were performed on Macaque monkeys (*macaca mulatta*), fully anesthetized with Dial (Ciba)\*, 45 cc. per kilogram body weight, part of the dose given intraperitoneally, part of it intramuscularly. Then the animal was tied down upon the operating-table with its head fixed in a special headholder<sup>3</sup> so that the head was oriented in a definite, constant position in space. One sensory motor cortex was then exposed, and with the micro-injection apparatus of Dusser de Barenne and Sager<sup>3</sup> concentric needle electrodes mounted on the barrel of a tuberculine syringe, were introduced into the desired thalamic nucleus. The needle-electrodes consisted of a hypodermic needle (gauge no. 25), with its tip ground off conically, through which passed the central wire electrode insulated to its tip. The central electrode protruded about 1½ mm. beyond the circumferential one. For recording the ETG the needle electrodes were connected to a D C amplifier and cathode ray oscillograph. After taking the normal ETG the three subdivisions of the sensory cortex were locally strychninized, *seriatim*, ending with the subdivision functionally related to the thalamic nucleus into which the needle had been introduced. An ETG was taken after each strychninization. The experiment was repeated on the opposite hemisphere. Then the animal was killed by injection of 100 cc. of 15% formalin into each of the carotids. Half an hour later the brain was removed and placed in formalin, 15-20 hours later the brain was sectioned (in the frontal plane) in slices 2 mm. thick and thus the location of the needle in the thalamus identified. In the second group of experiments the ECGs were taken simultaneously with bipolar electrodes from the various subdivisions of the sensory cortex (A C amplifiers, 4 element Westinghouse oscillograph), before and after intrathalamic strychninization. This was performed as described by Dusser de Barenne and Sager.<sup>3</sup>

The nomenclature of the thalamic nuclei used here, as in the paper by Dusser de Barenne and Sager, is that of C. Vogt<sup>4</sup> and Friedemann.<sup>5</sup> This choice is purely for the practical reason that these authors have provided the most complete series of illustrations of the *cercopithecus*' thalamus. There is no objection against this choice for the experiments on the macaque's brain since Le Gros Clark and Boggan<sup>6</sup> have found that "the cytoarchitecture of the thalamus of *Macaca* corresponds extremely closely with that of *Cercopithecus* as described and figured by Friedemann (1911-12)." For the designation of the various cortical areas used here we refer to a previous paper.<sup>4</sup>

\* The Dial was kindly put at our disposal by the Ciba Co.

## RESULTS

We shall begin with two experiments on nucleus Vb, in which the face alone is represented sensorially.<sup>3</sup>

Protocol of an experiment with strychninization of the postcentral cortex.

November 18, 1936. Macacus. 2.82 kg.

9.00 a.m.—1.3 cc. Dial ( $\frac{2}{3}$  of the dose intraperitoneally,  $\frac{1}{3}$  intramuscularly).

Exposure of *right* hemisphere. Concentric needle-electrodes into thalamus by transverse route, intended to reach nucleus Vb (face-nucleus), inclination 35°, depth 16½ mm. Central electrode to grid of amplifier, circumferential electrode (needle proper) to cathode.

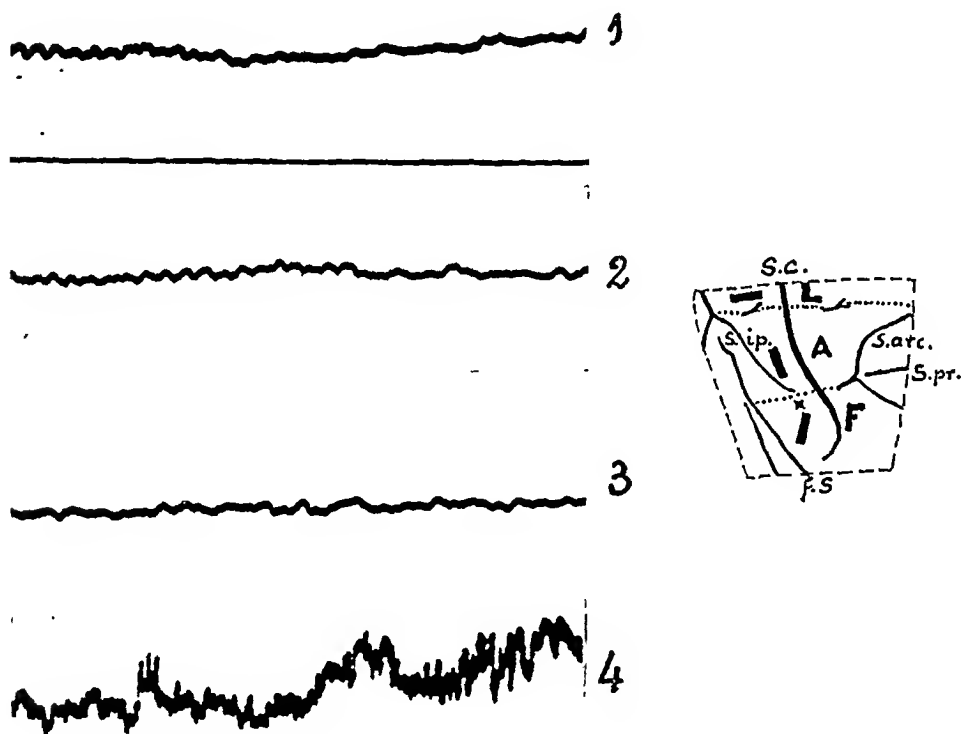


FIG. 1. Experiment of November 18, 1936. Macaque monkey. Dial narcosis. Electrothalamogram (ETG) recorded from nucleus Vb (face-nucleus). Record 1—control. Record 2—10 minutes after strychninization of postcentral leg-area. Record 3—10 minutes after strychninization of postcentral arm-area. Record 4—13 minutes after strychninization of postcentral face-area. Only in record 4 ETG shows "firing" of face-nucleus. Amplification in all records the same. Diagram indicates location of the 3 strychnine-applications and the site of entrance of the needle (x). The stippled lines indicate the boundaries between leg- and arm- (L and A) and arm- and face-subdivisions (A and F) of the exposed portion of the sensory cortex. Broken line indicates edge of opening in dura. S.c. =sulcus centralis; s.ip. =sulcus intraparietalis; f.s. =fissura Sylvii, s.arc. =sulcus arcuatus; s. pr. =sulcus principalis.

D.C. amplifier in combination with cathode ray oscillograph. Cambridge moving paper camera.

10.55. Record 1 (Fig. 1) taken with lowest amplification.

10.57. Strychninization of *postcentral leg-area* by applying across its width an oblong piece of filter paper, moist with 3 per cent strychnine-solution (dimensions of filter paper  $1 \times 3$  mm.).

11.07. Record 2 (Fig. 1) taken.

11.11. Strychninization of *postcentral arm-area* by application of a similar strip of filter paper to lower half of postcentral gyrus, parallel to central sulcus.

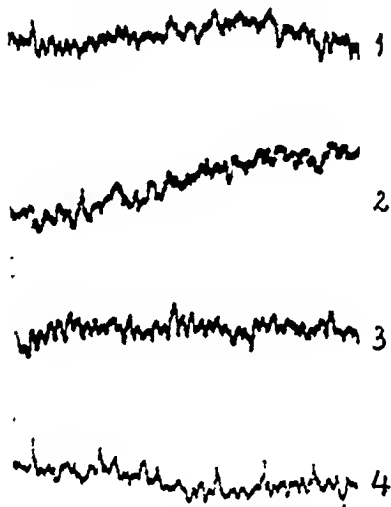


FIG. 2. Experiment of November 23, 1936. ETG of nucleus  $Vb_2$  (face-nucleus) of thalamus of macaca mulatta (Dial-narcosis) before (record 1) and after (records 2, 3 and 4) local strychninization of precentral sensory cortex, leg-, arm- and face-areas respectively. No apparent change in ETG of records 2 and 3 compared with that of record 1; definite "firing" in ETG in record 4, i.e., 11 minutes after local strychninization of precentral face cortex.

11.21. Record 2 (Fig. 1) taken.

11.23. Strychnine applied to *postcentral face cortex*.

11.36. Record 4 (Fig. 1) taken.

Autopsy: end of needle-track in nucleus  $Vb$  at level of Vogt's plate no. 5<sup>2,3</sup>.

In the following experiment the strychninizations were performed on the precentral sensory cortex.

November 23, 1936. Macaca mulatta. 2.80 kg.

9.15 a.m. 1.3 cc. Dial( $\frac{2}{3}$  of dose intraperitoneally,  $\frac{1}{3}$  intramuscularly).



- 11.30. Animal not fully under. .1 cc Dial intramuscularly.
  - 2.00 p.m. Animal completely anaesthetized.
  - 2.16. Exposure of *right* hemisphere. Concentric needle-electrodes into thalamus via transversal route, intended for nucleus Vb; inclination 35°, depth 20½ mm.
  - 2.19. Record 1 (Fig. 2) taken (amplification 3).
  - 2.21. Strychninization of *precentral leg*-area with filter paper 1×3 mm.
  - 2.32. Record 2 (Fig. 2) taken (same amplification as before).
  - 2.33½. Strychninization of *precentral arm*-area 4 with filter paper 1×3 mm.
  - 2.40. Record 3 (Fig. 2) taken (same amplification).
  - 3.09. Strychninization of *precentral face* cortex with filter paper (1×3 mm.) moistened with 3 per cent strychnine solution.
  - 3.20. Record 4 (Fig. 2) taken (same amplification as before.)
- November 24. *Autopsy*: needle-track ends in plane between C. Vogt's plates 5 and 6 in nucleus Vb<sub>2</sub>.

From these two and similar experiments it follows (1) that the local strychninization of the face-subdivision of the sensory cortex results in typical changes in the ETG of the face-nucleus (Vb); (2) that the local strychninization of any portion of the two other subdivisions of the sensory cortex does not produce any changes in the ETG of this nucleus; (3) that this nucleus is "fired" by the local strychninization of the precentral as well as of the postcentral portion of the face-subdivision of the sensory cortex.

The same obtains for the arm- and leg-nuclei, i.e., that each is "fired" only by the local strychninization of the pre- or postcentral portion of the subdivision of the sensory cortex corresponding to it.

There is one point which needs further elucidation, namely the apparent contradiction which was mentioned in our paper on "functional organization in the sensory cortex of the monkey" (4, p. 83). There it was reported that strychnine-spikes appear in the ECG of both the leg- and arm-subdivisions of the sensory cortex upon local strychninization of either L.6a or A.6a. Those observations have shown that so far as this distribution of the strychninespikes in the cortex is concerned no functional boundary exhibits itself between L.6a and A.6a. However, the contrast between this absence of the functional boundary, so far as the ECG is concerned, and its presence in regard to the symptoms of sensory excitation upon local strychninization of these same areas is not a contradiction, for the ECG expresses the activity of the cortex at that level of the CNS, whereas the symptoms of sensory excitation depend upon lower levels, notably the sensory nuclei of the optic thalamus, upon which converge all sensory impulses from the periphery of the body. At present we know that local strychninization of the sensory cortex "fires" the sensory nuclei of the thalamus, and in this respect one finds a definite functional boundary between L.6a and A.6a, for the leg-nuclei are "fired" by local strychninization of L.6a, but not by that of A.6a, whereas the arm-nuclei are "fired" by local strychninization of A.6a, but not by that of L.6a.

The following protocol serves as an illustration.

November 30, 1936. *Macaca mulatta*. 3.38 kg.

9.10. 1.52 cc. Dial (⅓ of dose intraperitoneally, ⅓ intramuscularly).

10.00. Animal completely under.

10.02. Exposure of *right* hemisphere.

10.05. Concentric needle-electrodes into thalamus via transversal route. Intention to

reach the dorsal portion of one of the arm-nuclei, lbIV or lbI (C Vogt), inclination 33°, depth 19 mm.

- 10 25. Record 1 (Fig. 3) taken (control) and then a series of records from various areas of the leg- and arm-subdivisions of sensory cortex  
 10 37 Local strychninization (1×3 mm) of leg area 6a (L 6a)  
 10 44 Record 2 (Fig. 3) taken with same amplification as in record 1 Subsequently a series of records from various areas of sensory cortex was taken (L 6a, L 4, L 2, A 6a, A 4, A 2, L 6a) \* Needle left in thalamus until afternoon  
 2 31 Record 3 (Fig. 3) taken as a control  
 2 40½ Local strychninization of arm-area 6a (A 6a)  
 2 45 Record 4 (Fig. 3) taken, followed by recording of ECG of various areas of the leg- and arm-subdivisions \*

December 1

*Autopsy* End of needle track in dorsal portion of nucleus lbI (Vogt's plate 6 (arm nucleus))  
*Conclusion* local strychninization of L 6a did not "fire" this nucleus, whereas local strychninization of A 6a promptly "fired" this nucleus Following the strychninization of L 6a (morning) and that of A 6a (afternoon) both entire leg- and arm subdivisions were "fired"



FIG 3 Experiment of November 30, 1936. ETGs of nucleus lbI (one of the arm-nuclei) of macaque's thalamus Dial-narcosis Record 1 taken before, record 2 after local strychninization of L 6a No change in ETG Record 3 taken before, record 4 after local strychninization of A 6a Prompt "firing" of nucleus lbI The entire leg- and arm subdivisions were fired by each of the two strychninizations

The second group of experiments mentioned above rounds out the picture of the direct functional interrelation of sensory cortex and thalamus In these experiments intrathalamic strychnine-injections were performed, using the micro-injection technique described previously,<sup>2,3</sup> and recording the ECG of various areas of the three subdivisions of the sensory cortex. The essential result in this group was that the injection of strychnine into any particular sensory nucleus of the thalamus "fired" that, and *only* that, subdivision of the sensory cortex, both precentral and postcentral, which subserves sensation in the *same* part of the body. This result must be interpreted as showing that in each particular nucleus of the thalamus, let us say, in each arm-nucleus originate thalamo-cortical neurons to terminate in the various areas of the arm-subdivision, and only of the arm-subdivision, of the sensory cortex; thus the strychninization of the perikarya of these neurons "sets on fire" the various areas of the arm-subdivision of the sensory cortex. The same re-

\* This part of the protocol considerably reduced

lation obtains between the leg- and face-nuclei of the thalamus and the leg- and face-subdivisions of the sensory cortex respectively.

Finally it must be stated that (1) local strychninization of white matter (e.g., corona radiata, internal capsule, corpus callosum) in our experience never "fires" grey matter; (2) local strychninization of masses of grey matter having no direct corticopetal connections with the sensory cortex (e.g., nucleus caudatus, medial nuclei of the thalamus) never "fires" this region of the cortex.

### DISCUSSION

Apart from the results, reported above, to which we shall return below, these experiments provide a check upon the extent, location and subdivision of the sensory cortex on the outer surface of the macaque's brain,<sup>1</sup> and upon the functional identification of the macaque's sensory nuclei in the thalamus.<sup>3</sup> In this connection two crucial findings should be reported here: 1. local strychninization *without* the sensory cortex never "fired" the face-, arm- or leg-nuclei of the thalamus; 2. local strychninization anywhere *within* the sensory cortex never "fired" the *medial* nuclei of the thalamus (mag, mapt, mapl, maga, magp, ma).

Together, all the results of the present investigation are in entire harmony with the results of the previous work and complete the confirmation of the two hypotheses advanced in 1924<sup>1</sup> to explain how strychninization of only a few square millimeters of the sensory cortex induces symptoms of sensory excitation in a large portion of the body. That local strychninization of grey matter in the CNS with recording of the electrical activity of grey matter in the CNS reveals directed functional relations has been shown in a previous paper.<sup>4</sup> Therefore, the only construction which can be put on the facts here established by *physiological* methods is that there exist between the sensory cortex and the sensory nuclei of the thalamus directed functional relations: 1. from each subdivision of the sensory cortex to, and only to, the corresponding sensory thalamic nucleus or nuclei, 2. from each sensory thalamic nucleus to, and only to, the corresponding subdivision of the sensory cortex. This is schematized in Fig. 4.

The three principal features in this diagram are:

1. the essential similarity of the three sensory systems for face, arms and legs;
2. that each system after reaching the cortex feeds back into the thalamus;
3. that throughout the entire course of these three systems functional boundaries are maintained.

The diagram shows these boundaries only for one frontal plane, but it must be pointed out that they are present throughout the entire fronto-occipital extent, both in the thalamus and in the cortex. Thus the boundary indicated in the diagram between the leg- and arm-subdivisions of the sensory cortex extends all the way from the interparietal sulcus to the anterior

margin of area 6a, as represented in the diagrams of the extent, location and subdivision of the sensory cortex previously given<sup>1,4</sup>

The apparent contradiction mentioned on p. 180 leads to an important point. Two observations are relevant here:

1. So far as the cortical distribution of the strychnine-spikes in the leg- and arm-subdivisions upon local strychninization of L.6a or A.6a is concerned, no functional boundary between the two subdivisions exhibits itself.

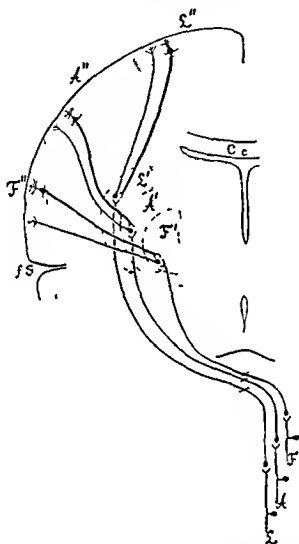


FIG 4 Diagrammatic representation of the organization of the three main sensory systems (for the legs, arms and face) All internuncial neurons between the subthalamic sensory neurons and the thalamo cortical neurons have been omitted, to simplify as much as possible the diagram

2. Notwithstanding the fact that both entire leg- and arm-subdivisions of the sensory cortex are "fired" by local strychninization of either L.6a or A.6a, an animal, when "clinically" observed (without narcosis), discretely refers his symptoms of sensory excitation (paraesthesiae, hyperaesthesia and hyperalgesia) to the legs, and *only* to the legs, after local strychninization of L.6a, and conversely to the arms, and *only* to the arms, after local strychninization of A.6a.

These observations throw new light on the observation of Dusser de Barenne and Sager that the symptomatology after local intrathalamic strychn-

ninization in the acutely and totally decorticated cat was indistinguishable from the symptomatology in the animal with cortex intact. From that observation the authors concluded that in the case of strychninization of the thalamus "the sensory cortex plays no role in the elaboration of the ensuing sensory disturbances" (2, p. 246).

In this respect the cortex is (in the cat) not only unnecessary but is even unable (in the monkey!) to distort the distribution of the sensory disturbances determined by the hyperactive thalamic nucleus or nuclei. The functional boundaries remain. For the "firing" of the two entire leg- and arm-subdivisions of the sensory cortex by local strychninization within either L.6a or A.6a does not deter the animal from projecting his sensory disturbances discretely upon that part of the body subserved sensorially by the particular thalamic structure "fired" by the feed-back from the strychninized cortical area.

It follows that the part of the body to which the animal refers his symptoms of sensory excitation is determined *not* by the subdivision or subdivisions of the sensory cortex "fired," but by the thalamic nucleus or nuclei "fired" by the direct feed-back from the strychninized area of the sensory cortex.

Thus, though both hypotheses advanced by Dusser de Barenne in explanation of his observations in 1924 have been substantiated, the second hypothesis, namely that local strychninization of any subdivision of the sensory cortex "sets on fire" the corresponding thalamic nucleus or nuclei, is evidently the crucial one. For all these observations and considerations imply not only the predominance of the thalamus in sensation, but that this last subcortical sensory station determines the reference of sensation by the individual, even contrary to coexisting cortical activity.

We must now discuss briefly the hypotheses of Head and Holmes<sup>6</sup> concerning the functional interrelation of the thalamus and cortex in the production of sensation.

In their well-known diagram (6, p. 172) they represent an internuncial neuron from the ventro-lateral region of the thalamus to the medial nuclei, which they regard as the "essential center" of the thalamus. The cortico-thalamic neurons ending in the ventro-lateral region of the thalamus exert, according to Head and Holmes, an inhibitory influence upon this region of the thalamus. They assume that with interruption of these cortico-thalamic fibers the activity of the thalamus is released from its normal cortical restraint, and that the afferent impulses, reaching the ventro-lateral region of the thalamus, flow over uncontrolled to the medial thalamic region, which "is the centre of consciousness for certain elements of sensation" (l.c. p. 181), "mainly occupied with the affective side of sensation" (l.c. p. 180).

This attractive conception, however, is open to criticism. Although in the cat the medial nuclei are endowed in some way with sensory functions<sup>7</sup>, this is not so in the monkey<sup>8</sup>. Apparently in this respect evolution of thalamic structures and functions has resulted in a definite shift. It is highly

improbable that in the evolution of the human brain phylogeny should have reversed itself, backward toward the stage of the cat instead of onward from the stage of the monkey. In the second place the inhibitory function of the cortico-thalamic pathways is by no means established; in fact it was and is purely hypothetical. In all experiments presented here the strychninization of a number of the cells of origin of these cortico-thalamic neurons in the sensory cortex resulted in a "firing" of the corresponding thalamic nuclei, just as, in the earlier experiments of Dusser de Barenne<sup>1</sup>, it resulted in symptoms of sensory excitation. These are results which are the reverse of what could be expected on the basis of the hypotheses of Head and Holmes. Yet there may be some truth in them, for we have found that the local strychninization of two particular regions, areas 4-s and 1, of the monkey's sensory cortex results in a temporary suppression of the electrical activity of area 4<sup>1</sup>. However, this suppression in the case of area 4-s does not depend upon the direct cortico-thalamic connections which Head and Holmes had in mind and with which the present paper dealt. This suppression involves indirect cortico-thalamic relations and must be taken up in a subsequent paper.

#### SUMMARY

The present paper deals with two groups of experiments:

1. the effect of local strychninization of the sensory cortex upon the electrical activity of the optic thalamus, i.e., upon the electrothalamogram (ETG),
2. the effect of local strychninization of the sensory thalamic nuclei upon the electrical activity of the sensory cortex, i.e. upon its electrocorticogram (ECG).

In the first group with local strychninization of the cortex it was found that each thalamic nucleus is "fired" from that, and only that, subdivision of the sensory cortex, subserving sensation in the same part of the body. In the second group of experiments it was found that local strychninization of any particular sensory thalamic nucleus "fires" that, and only that, subdivision of the sensory cortex which subserves sensation in the same part of the body.

Sharp functional boundaries exhibit themselves between the adjoining sensory systems.

The discussion indicates the significance of these observations in regard to the dominance of the thalamus over the sensory cortex in sensory disturbances, even when initiated by excitation from the sensory cortex.

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# LIMITS OF VARIATION OF THE SYNAPTIC DELAY OF MOTONEURONS

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THE MINIMAL duration of the synaptic delay of ocular motoneurons has been determined (1935a) with sufficient accuracy, but considerable difficulties have been found in measuring its maximal duration. Experimental results (1935d) indicated that the maximal delay is not much longer than the minimal delay, and that the expected small variations could scarcely be measured in the original preparation, in which the responses were recorded from the internal rectus muscle (1935d, p. 527). A sufficient degree of accuracy has now been attained by recording the responses from the trochlear nerve.

Eccles (1936, 1937) has shown that the synaptic time in the superior cervical ganglion also is rigidly fixed within narrow limits, but it may be slightly shortened by creating facilitation or it may be lengthened by setting up refractoriness of the ganglion cells. Although in a different time scale, identical results are obtained with the trochlear motoneurons.

## TECHNIQUE

The observations here reported have been made on the oculomotor preparation of the rabbit (1935a, 1938a), the responses being recorded from the trochlear nerve. The synaptic delay is calculated by subtracting from the total latency of the F response 0.7 msec., which is the conduction time of the impulses from the F electrodes to the motoneurons, plus the conduction time from the motoneurons to the recording electrodes. The latter can be determined with sufficient accuracy by stimulating the motoneurons with short induction shocks, but the former must be estimated. Since the F electrodes are placed at about 10–15 mm. from the motor nucleus, the possible error is of the order of 0.1 msec.; for this reason two figures (0.5–0.6 and 0.8–0.9) are given for the durations of the extreme synaptic delays; the true value is doubtless within the range of these figures.

## RESULTS

Delivery of a shock through the F electrodes causes the arrival to the motoneurons (*M. N.*, Fig. 1, I) of an initial volley of impulses (*f*) followed by a series of volleys delayed during their passage across internuncial neurons (*i*). The temporal course of the arrival of the impulses is indicated in Fig. 1, II.

A number of motoneurons respond to the *f* impulses and eventually other motoneurons respond to the *i* impulses. The latency of the *f* wave (Fig. 4, *f*) is equal to the synaptic delay at the motoneurons, plus conduction time in the *f* fibers and in the motor nerve. The latency of the *i* wave includes in addition the synaptic delay at internuncial neurons. The appearance of the *i* wave depends on a number of conditions, among them being the state of

\* The experiments reported in this paper were carried out at the Central Institute for the Deaf, St. Louis, Mo., and were aided by a grant from the Rockefeller Foundation.



the preparation, which determines the amount of tonic internuncial bombardment of the motor nucleus. Thus in the experiment illustrated by the records of Figs. 2 and 4, at the start the response contained only an  $f$  wave (Fig. 2, 7, 8), while later (Fig. 4, 3, 6, 13) the  $i$  wave was almost as large as that of  $f$ .

The  $f$  wave, although of very short duration, is not a synchronous spike, which indicates the existence of slight differences in the delays at the individual motoneurons, there being a convincing reason to believe that the neurons with the longer synaptic delays are those stimulated at or only slightly above threshold. If the  $F$  shock is weakened (Fig. 2, 7, 8) the latency of the responses increases slightly or at least its crest appears later. The differences between the maximal and the minimal synaptic delays in submaximal responses, such as that in Fig. 2, 8, is doubtless not greater than 0.2 msec., and consequently the longest synaptic delay in these responses may be calculated at 0.8–0.9 msec. This also may be regarded as the maximal synaptic delay at trochlear motoneurons, because the responses in record 8 include a number of motoneurons stimulated at threshold. However, this statement, although valid for the majority of the motoneurons in the nucleus, may not be applicable to all the motoneurons, because the action potentials of the smallest axons in the trochlear nerve scarcely would be detectable at the amplification used for obtaining the records shown in Fig. 2.

A more conclusive proof of the existence of an upper limit for the dura-

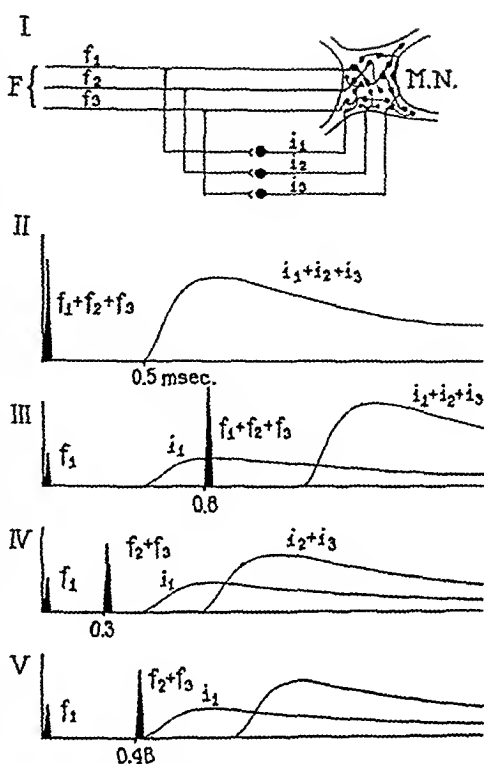


FIG. 1. Diagrams explaining the conditions of stimulation of the ocular motoneurons by delivery of shock through the  $F$  electrodes (cf. 1938b, Figs. 1 and 2).

I.  $f_1, f_2, f_3$ , fibers of the posterior longitudinal bundle;  $i_1, i_2, i_3$ , internuncial neurons, each cell actually representing a chain of neurons (1938b, Fig. 3). M.N., motoneuron with synaptic knobs.

II. A maximal shock capable of stimulating fibers  $f_1, f_2$ , and  $f_3$  causes the arrival to the motor nucleus of an initial volley of impulses ( $f_1+f_2+f_3$ ) followed by volleys of internuncial impulses ( $i_1+i_2+i_3$ ). The ordinates indicate the number of impulses, the abscissae the time of arrival, measured from the start of their spike potentials.

III, IV, and V. The maximal shock is preceded at the intervals 0.8, 0.3 and 0.48 msec. by a smaller shock capable of stimulating fiber  $f_1$  only. It is assumed that the refractory period of all  $f$  fibers is 0.52 msec. For the sake of simplicity it is assumed that the  $i$  volleys are not increased by facilitation.

tion of the synaptic delay is derived from the study of its lengthening during refractoriness (cf Eccles, 1937) due to penetration of an antidromic impulse into the soma of the motoneurons. When a shock is delivered to the motor nerve at progressively decreasing intervals before the testing F shock (Fig 3, 1 to 9), the response is seen to decrease in size at the same time that its latency increases. However, the height drops much faster and the response disappears before the latency has increased by more than 0.2 msec (cf records 1 and 8 in Fig 3). It is remarkable that the maximal value of the synaptic delay of the *f* response to weak stimuli is equal, as near as it can be measured, to the delay of responses to strong stimuli elicited during refractoriness.

Thus seems to establish a definite relationship of the synaptic delay, on the one hand, to the strength of the stimulus, and on the other hand, to the threshold of the motoneuron. Reduction of the strength of the stimulus, i.e., decrease of the number of activated synapses, or the raising of the threshold of the motoneuron causes lengthening of the synaptic delay, and although the variation is small it may have theoretical significance.

However, it must be admitted that the experimental evidence is not entirely conclusive. The fact that refractory motoneurons respond demonstrates that when their threshold is normal, the synaptic stimulus is supermaximal, i.e., that a number of synaptic knobs larger than the necessary minimum is activated. Since the *f* volley is not perfectly synchronous, the possibility exists that during refractoriness the initiation of the impulse takes place in a zone of the soma located under knobs receiving late *f* impulses or creating an excitatory process of longer duration than the shortest (cf 1938a).

The synaptic delay of responses to shocks of about twice threshold strength cannot be shortened in an appreciable manner by further strengthening of the shock, even if it is accompanied by a substantial increase in the number of responding motoneurons. But facilitation due to previous stimulation may shorten the latency, although by not much more than 0.1 msec. This is well shown by records 8 and 9 of Fig 2 and records 12 and 13 of Fig 4. Records 1 to 7 of Fig 2 demonstrate that during the period of facilitation the shorten-

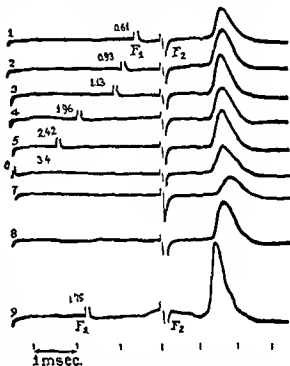


FIG 2 Oculomotor preparation, responses recorded from the trochlear nerve (2736). Testing shock (F2) 300 per cent stronger than the conditioning one (F1), for records 8 and 9 shock strength 30 per cent greater than for records 1 to 7. The latencies to the responses to F2 in record 7 and to F1 in record 9, include the maximal synaptic delay the latency to F2 in record 9 the minimal delay. The synaptic delay is calculated by subtracting from the total latency 0.7 msec, which is the conduction time of the impulses in fiber paths. Time in 0.2 and 1 msec below. Interval between shocks indicated in msec in records 1 to 6 and 9.

ing of the delay is in direct relation to the increase in the height of the response.

An examination of diagram I of Fig. 1 yields the explanation. This diagram reveals that even maximal stimulation of the bundle of *f* fibers cannot result in maximal stimulation of the motoneurons, because there are many synaptic knobs which, belonging to *i* cells, cannot be activated unless those cells are made to fire. Obviously, the only possibility of maximal stimulation of motoneurons consists in delivering two F shocks in succession. The first F shock (cf. 1935c, 1938b) creates a certain amount of internuncial activity and thus the impulses of the *f* volley of the second F shock may summate with internuncial impulses (Fig. 1, III). If the internuncial bombardment is strong enough, some motoneurons will have all their synapses simultaneously activated and the stimulation will be maximal. In fact, in some cases the stimulation is so strong that it causes the motoneurons to fire impulses into their axons immediately after completion of the absolutely refractory period (1935b).

As the effect of facilitation and that of a rise in threshold are in opposite directions, they may compensate each other. For example, in Fig. 3, the latency of the response (record 10) was shortened by facilitation (record 11) so that it became a synchronous nerve spike; but refractoriness (record 12) brought the latency back to its original value, or perhaps something less, because the speed of conduction in the motor axons may have been slightly subnormal.

On examining diagrams I and III of Fig. 1 it is realized that the shortening of the synaptic delay by facilitation involves a dual mechanism. On the one hand, facilitation increases the total number of impulses delivered to each motoneuron; and on the other hand, the *f* impulses of the testing shock arrive at the motoneurons some time after *i* impulses of the conditioning shock, so that the *f* impulses complete

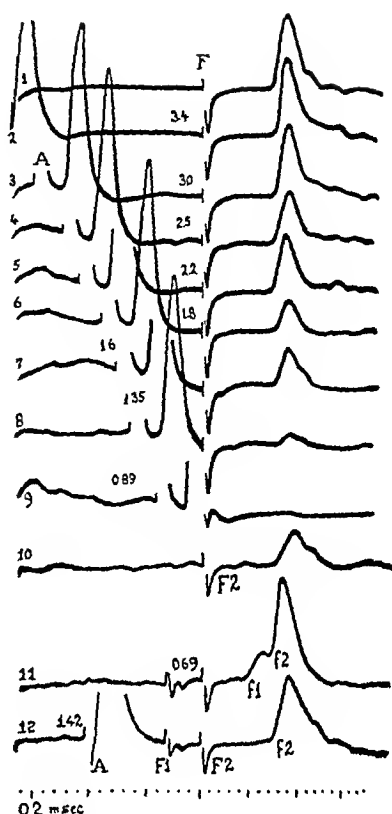


FIG. 3. Oculomotor preparation; responses recorded from the trochlear nerve.

Records 1 to 10 (2-2-36); a maximal antidromic shock (A) is delivered to the motor nerve at the intervals indicated in msec. before the testing F shock. The F response, shown unconditioned in record 1, diminishes in height and appears after lengthened latency.

Records 10 to 12 (2-6-36); the response to a testing F2 shock (record 10) is facilitated by delivery of a smaller F1 shock (record 11), its latency also is decreased, but delivery of a maximal antidromic shock (A) 1.42 msec. before F1 obliterates the response to this shock and lengthens the latency of the response to F2 (record 12). Time in 0.2 and 1 msec. below.

the stimulation initiated by the  $i$  impulses. That under such conditions the shortening of the delay is so slight is remarkable, and it must be related to the shortness of the period of effective summation of impulses arriving at neighboring synapses (1935d).

A direct examination of the problem has been carried out by the method of fractionation of the F volley (1935c), successfully applied by Eccles (1937) to the study of synaptic delays in the superior cervical ganglion.

In the experiment illustrated by the records of Fig. 4, two F shocks were delivered in succession. The conditioning shock ( $F_c$ ) was slightly subthreshold and in diagrams III to V of Fig. 1 is supposed to have stimulated only fiber  $f_1$ ; the testing shock was five times as strong and is supposed to have stimulated the whole bundle of F fibers. In constructing diagrams III, IV and V it also has been assumed that the absolutely refractory period of the  $f$  fibers measures 0.52 msec. (1935b).

Records 1 to 7 of Fig. 4 demonstrate that at intervals  $F_c$ - $F_t$  of 0.25 msec. or less the latency of the response was reduced, the shortening being greatest but still less than 0.2 msec. at the interval of 0.2-0.25 msec. At 0.29 msec. (record 8) the shortening was markedly less, and there was no shortening at the interval of 0.36 msec. (record 9). Obviously, the period of summation of the  $f_1$  and  $f_2+f_3$  impulses was shorter than that interval.

Increase of the interval between shocks soon resulted in increase of the response. Facilitation was demonstrable at an interval of 0.48 msec. (record 10); since at that time the  $f_1$  fibers (Fig. 1, V) were still refractory, the increase of responses was due to summation of the  $f_2+f_3$  impulses with  $i_1$  impulses which arrived later. The latency, measured from the moment of delivery of the  $F_t$  shock, was of course not shortened. But at longer intervals (records 11 and 12; cf. Fig. 1, III) the  $f_1+f_2+f_3$  impulses were summing with  $i_1$  impulses which had arrived previously, and the response not only was larger but also had a shortened latency.

It is important to note that the latency in records 7 and 12 is the same, a fact that was to be expected, because in both cases the response was due to the summated effect of impulses arriving in quick succession.

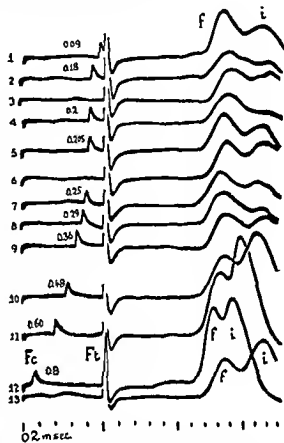


FIG. 4. Same experiment as in Fig. 2 but two hours later. Conditioning shock ( $F_1$ ) one-fifth of the testing shock ( $F_2$ ). Intervals between shocks indicated in msec. on the records. 3, 6, 13, unconditioned responses to  $F_2$ . Conditions of the experiment indicated in Fig. 1.  $f$ , response to the  $f$  impulses;  $i$ , response to the  $i$  impulses. Time in 0.2 and 1. msec. below.

Comparison of the  $f$  waves of records 12 and 13 among themselves and with the time line shows the slight amount by which the delay of an impulse at one synapse may be reduced; but comparison of the  $i$  waves in those records reveals that if the impulse has to cross successively several facilitated neurons, the shortening may be considerable. In that case, where the impulses started by the Ft shock were obliged to cross first the  $i$  synapses and then the synapses on the motoneurons, the shortening amounted to about 0.4 msec.; but if they had to cross through three facilitated synapses the shortening would have been equal to a whole synaptic delay (0.6 msec.), and consequently the same as is obtained by "skipping" a synapse (1935c, Fig. 3, 20, 21).

### DISCUSSION

The delay of transmission of an impulse across synapses on the motoneurons varies between very narrow limits, the maximal variation being about 0.3 msec. In facilitated responses the delay measures 0.5–0.6 msec. and in threshold responses, 0.8–0.9 msec. However, it is possible that the limits of variation may be even smaller, because in the present measurements no correction has been introduced either for latencies of the  $f$  impulses at the F cathode, or for subnormal speed of conduction of the impulses in motor axons made refractory by the antidromic shock. With the present technique the amount of correction cannot be estimated, and therefore it is advisable to take the obtained figures as they stand and summarize the results in the following sentence. *A motoneuron stimulated by a volley of impulses delivered at its synapses either responds within 0.5–0.6 to 0.8–0.9 msec., or it does not respond unless restimulated by a new volley of impulses.*

The rigidity of the synaptic delay must be carefully taken into account in establishing the theory of synaptic transmission, for it is obvious that no excitatory process may be assumed which does not take place within that interval of time, as it is never finished in less than 0.5–0.6 msec. after arrival of the impulse or in more than 0.8–0.9 msec.

For descriptive purposes the synaptic delay is measured from the beginning of the arrival of the stimulating impulse at the synaptic knob, a procedure which masks the true time relations between stimulus and response. The stimulus, *i.e.*, the impulse delivered at the synapse, is not an event of vanishingly short duration; indeed, it has a duration which approaches and may even be as long as the synapse time itself.

According to Gasser and Grundfest (1936) the spike potential that accompanies the impulse along mammalian A fibers has a duration of about 0.5 msec. This must also be the duration of the spike in the  $f$  fibers, because judging by their threshold and refractory period these fibers belong to class A (1935a). Since the  $f$  fibers upon entering the motor nucleus branch out and diminish in caliber, it may be argued that their spike potential is lengthened, but at any rate no great lengthening may be assumed for the reason that a second effective impulse can be transmitted through synaptic terminals when started 0.52 msec. after the first (1935b) and it is believed that the ab-

solutely refractory period ends when the major part of the spike is finished (Adrian, 1921, Gasser and Grundfest, 1936). A new kind of response at the synaptic knobs can scarcely be admitted, because the knobs are not always found at the end of the fibers, in fact, they are often situated in the trajet of long fibrils (1938a). Under conditions such as these it seems reasonable to assume that the major part of the spike, at least at some synaptic knobs known to be capable of setting up a response, lasts for about 0.5 msec. This, it will be noted, is the duration of the minimal synaptic delay, so that the conclusion becomes unavoidable that when these knobs are effective the stimulated neuron fires its own impulse at the moment when the spike potential at the knobs has subsided or finds itself at an advanced point of the descending phase. It may even fire 0.3 msec later. Whether the latter is due to the fact that the spike potential at some knobs is of longer duration or that the volley of  $f$  impulses is slightly asynchronous, or is in fact due to a true delay in the setting up of the new impulse, cannot be decided at present. However, on the evidence available, especially the fact that the raising of the threshold lengthens the synaptic delay, it would not be unreasonable to assume that a true delay of that value may take place.

Emphasis must be laid upon the fact that the summation of impulses delivered in succession at neighboring synapses cannot reduce the synaptic delay below a minimal value, which is but slightly less than the delay observed after stimulation by a large synchronous volley of impulses. This indicates that the second impulse does not bring to completion the process started by the first, the second starts its own local process (cf. 1938a), which does not result in the setting up of the new impulse until the spike potential at its synaptic knob has subsided or is near completion.

### CONCLUSIONS

1 The limits of variation of the synaptic delay of ocular motoneurons have been determined with an improved technique.

2 The average delay measures 0.7 msec. It may be shortened by facilitation or by increasing the number of activated synapses, and it may be lengthened by decreasing the stimulus or by raising the threshold of the motoneurons.

3 The minimal synaptic delay measures 0.5–0.6 msec, and the maximal delay 0.8–0.9 msec.

4 It may be calculated that the minimal synaptic delay is equal to the duration of the major part of the spike potential at the synaptic knobs.

5 Knowledge of the temporal course of synaptic transmission is not sufficient to identify the elementary process underlying transmission, but it reduces the number of possible assumptions. No process may be assumed that cannot take place within the now known rigid time constants.

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# SYNAPTIC STIMULATION OF MOTONEURONS AS A LOCAL PROCESS

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THREE lines of evidence justify the assumption that the initiation of an impulse by synaptic stimulation of a motoneuron is attributable to a process reaching threshold within a discrete zone of the soma, underneath a group of active synaptic knobs. (1) The soma of the motoneuron is electrically excitable and has a number of properties in common with peripheral nerve fibers. It must conduct propagated disturbances according to the all-or-nothing law, while subliminal disturbances must remain localized (1935d), i.e., their spread away from the stimulated zone must be decremental, as is known to be the case in nerve (Hodgkin, 1937; Lorente de Nó, 1938a; cf. Eccles, 1936, 1937). (2) The period of effective summation of two volleys of impulses arriving in succession at different synapses is brief and summation does not essentially alter the time course of stimulation by the second volley (Lorente de Nó 1935b, c, 1938b, c; cf. Eccles, 1937). (3) Activation of a large number of synapses belonging to a certain set of pathways remains ineffective in the absence of bombardment of the motoneurons by impulses that have originated in internuncial pools of neurons (Lorente de Nó 1935c, p. 507; 1938c, Fig. 7, 13 to 20).

The last line of evidence is doubtless the more direct one, and further experiments conducted on this basis have yielded results that seem to be unequivocal. These findings are presented here, together with anatomical data on the distribution of synaptic junctions on the soma of the motoneurons, which are necessary for an understanding of the facts observed.

## TECHNIQUE

The experiments have been carried out on the oculomotor preparation of the rabbit, as previously described (1935a, 1938c). The anatomical studies have been conducted on the brainstem and spinal cord of young cats, and the specimens were stained with silver chromate after Golgi.

## RESULTS

*Experimental.* During mild ether narcosis, not deep enough to modify the corneal reflex in an appreciable manner, but still sufficient to reduce or abolish the tonic labyrinthine innervation of the eye muscles, single F shocks are ineffective in setting up a synaptic response of ocular motoneurons, even when they are so strong that they must stimulate every fiber of the posterior

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longitudinal bundle and adjacent pathways. Under these conditions it cannot be doubted that a large number of synapses on the motoneurons are activated. In point of fact, in the absence of ether, large numbers of motoneurons, and eventually the total population of the motor pool, do respond. The absence of response during narcosis cannot be attributed, at least not wholly, to a direct effect of ether on the motoneurons, for the following reasons: (1) When two F shocks are delivered in succession at the proper interval, the second sets up responses that include large numbers of motoneurons (Figs. 1 and 2). (2) During ether narcosis shocks delivered to the nuclei of the reticular substance in front of the oculomotor nuclei set up synaptic responses of the motoneurons (1938d, Fig. 2). (3) Single F shocks are rendered ineffective if the vestibular nuclei and the reticular formation in the medulla are destroyed. (1935c.) (4) Single F shocks also remain ineffective if previous stimulation has temporarily suppressed the normally existent background of subliminal bombardment of the motor nucleus by internuncial impulses (1936, 1938c, Fig. 7).

In conditions such as these the conclusion is unavoidable that the activation of any number of *f* synapses in isolation is insufficient to stimulate the motoneurons to discharge impulses into their axons. A typical experiment is illustrated in Fig. 1. Two shocks in succession were delivered: F2 had twice the strength of F1; F1, in the absence of ether narcosis, was almost maximal for the F response to single shocks (Fig. 1, 11 and 15). During ether narcosis both F1 and F2 delivered in isolation were ineffective (Fig. 1, 1), but when F2 was preceded by F1, at intervals of 0.6 to 5 msec., it was followed by strong responses, which at certain intervals (Fig. 1, records 3 and 4) had almost half the size of the maximal motor twitch (record 10). A few minutes after discontinuing the narcosis, both F1 and F2 were individually able to set up strong responses (records 13 and 15), and when delivered in succession at intervals of 0.6 to 5 msec., the F2 response also was facilitated.

The facts described below are significant. At intervals of 0.41 msec. (record 1) or 0.48 msec. (record 11) the F2 shock was ineffective, either in setting up

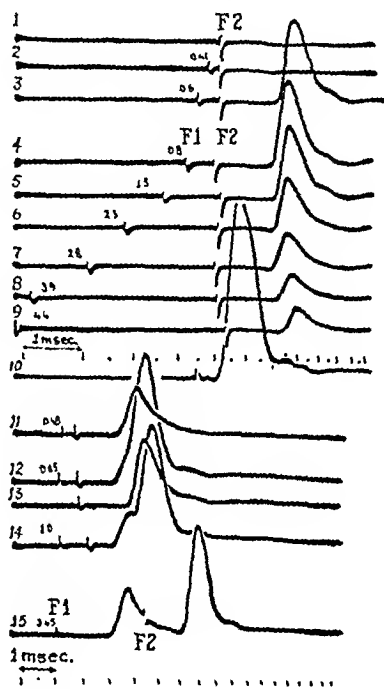


FIG. 1. Oculomotor preparation of the rabbit. Response recorded from the internal rectus muscle (6-11-36). Conditioning shock (P1) 50 per cent of the testing shock (F2). Intervals between shocks indicated in msec. on the records. Light ether narcosis for records 1 to 9; no narcosis for 11 to 15. 10, maximal motor twitch.

any response at all, or in adding anything to the response produced by F1 (cf. records 11 and 15). However, at 0.6 msec. (record 3) or 0.65 msec. (record 12), the F2 response was large, indicating that between the intervals of 0.41–0.48 to 0.6–0.65 msec. a change in the excitability of the motoneurons had taken place. Since in both records 3 and 12 the F2 response had the minimal synaptic delay, there is no doubt that in both cases the F2 response had been produced by *f* fibers not reached by the F1 shock, for the absolutely refractory period of *f* fibers is 0.52 msec. (1935b) and the impulses set up in refractory fibers by the F2 shock arrive at the motor nucleus after some delay and set up responses after lengthened latencies (1935b; cf. Fig. 2, 11). The increase in excitability was so great that in the case of record 3 a limited number of *f* fibers set up a large response after the minimal synaptic delay (cf. 1938b, Fig. 1), while in record 1, a more powerful volley of *f* impulses was unable to fire any motoneuron. On the other hand, as the response in record 3 was caused by fibers not stimulated by F1, the change in excitability cannot be ascribed to repetitive stimulation of synapses.\* Under conditions such as these the only plausible assumption is that internuncial neurons responded to the impulses set up by the F1 shock (cf. 1938b, Fig. 1), and that these internuncial impulses when added to the *f*2 impulses were capable of stimulating the motoneurons to discharge. Therefore, it must be concluded that the *f*1 impulses, although they were unable to fire motoneurons, could fire internuncials; and that the internuncial impulses alone were incapable of firing motoneurons.

The same facts are presented in a more striking manner by the records shown in Fig. 2, which belong to another experiment. For the series of records 12 to 17, since F2 had twice the strength of F1, the same conditions were created as were present in the case of Fig. 1, 1 to 9, and identical results were obtained. It will be noted that the response at the start of the period of facilitation (record 13) had the minimal synaptic delay, and consequently was caused by impulses conducted by the fibers not reached by F1.

\* In the absence of ether narcosis, when the excitability of internuncial neurons is high, facilitation has been observed to begin 0.43–0.48 msec. after delivery of F1, i.e., at a moment when all the fibers stimulated by F1 were still absolutely refractory (1935c, 1938d).

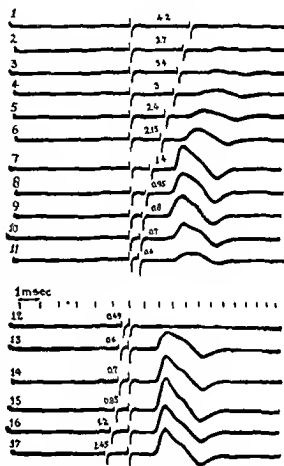


FIG. 2. Oculomotor preparation. Responses recorded from the internal rectus muscle (6-4-36). Light ether narcosis throughout. Intervals between shocks indicated in msec. on the records. The larger shock was maintained at a fixed position at the center of the oscillograph, while the smaller shock, 50 per cent of the larger one, was progressively displaced.

In the case of records 1 to 11, the F2 shock preceded the smaller F1, so that repetitive stimulation of  $f$  fibers was necessary to produce the response. It will be seen that at the 1.4 msec. interval, when it was expected that a large number of  $f$  fibers had recovered the response (record 7) was practically identical with that shown in record 17. But at shorter intervals the responses in series 11 to 8 were consistently smaller than those at the same intervals in series 13 to 16. They were also delayed, which indicates that the  $f$  impulses had been conducted to the motor nucleus with subnormal speed. As a matter of fact, the series of records 11 to 7 is like that regularly obtained with the nerve-muscle preparation after delivery of two shocks at similar intervals. This result can be graphically expressed in a simple manner. The internuncial discharge started by the conditioning shock created a subliminal stimulation of the motoneurons, so that the motoneurons responded to every  $f$  impulse that they received, with the result that the number of responding motoneurons became proportional to the number of recovered  $f$  fibers. Thus we have the following facts: (1) in record 1 a maximal  $f$  volley was unable to set up a response, while in records 13 and 11 small  $f$  volleys did produce responses; (2) in records 11 to 8 the numbers of responding motoneurons were roughly proportional to the numbers of the  $f$  impulses. The conclusion lies at hand that the strength of stimulation of motoneurons depends not only on the number of simultaneously activated synapses, but also on other conditions, one of which must be the topographical distribution of the synapses over the soma of the motoneuron.

*Anatomical.* It is at present generally recognized that the synapses on the motoneurons are formed by small thickenings of nerve fibers, located on the body and dendrites.\*

The synaptic thickenings have been designated in the literature by various terms, which as a rule include the adjective "terminal" and often the noun "feet," for instance, the end or terminal feet of Held. Recently the designation, *boutons terminaux*, used in the French translation of Cajal's book (1909) has been widely employed. Given the extreme variety of forms of the thickenings of the axon (cf. Cajal, 1935), any term already used to designate another object is obviously improper, but this impropriety is unavoidable in the present case. Here the term "knob," suggested by Auerbach, is used. The adjective "terminal" also is improper, and even more, it is misleading; here use is made of the non-committal designation "synaptic."

The distribution of the synaptic knobs on the motoneurons and other multipolar neurons has in the past been studied in stains made with reduced silver according to the methods of Cajal, Bielschowsky, or their modifications which, however, yield only incomplete pictures and as a rule give the impression that each knob forms the ending of a fibril. It is exceptional to obtain pictures which demonstrate the fact that several knobs belong to a single fibril. But even in the best anatomical picture ever published (Cajal, 1909, Fig. 436), the distribution of all the knobs belonging to each of the fibrils cannot be observed. Ordinarily, the silver picture is incomplete on another count; it fails to show many of the knobs present on a cell, and even all the knobs on by far the largest number of cells in the gray matter. For example, many of the knobs reproduced in Figs. 3 and 4,

\* In some cells, such as the Purkinje cells of the cerebellum, the synapses extend to the initial segment of the process called axon. The same seems to be true for some types of internuncials in the spinal cord. As the axon often starts from dendrites at considerable distances from the body of the cell, it is a matter of definition whether to place the origin of the axon at the cell body and to consider that its initial part may carry synapses, or to hold that the axon starts at the level of ending of the synaptic scale of the cell.

in point of fact all those establishing synaptic junctions on dendritic branches, are not stained or cannot be identified with the use of the ordinary silver stains

The silver staining methods are, of course, capable of improvement, and the yield obtained is in relation to the experience and knowledge of the worker using them. No theoretical reason exists why it should be impossible eventually to stain any synaptic junction with reduced silver. But in the experience of the present author, the silver chromate method of Golgi is the only one known to be capable of staining simultaneously and completely the synaptic knobs and the fibers to which they belong. Satisfactory stains can be obtained of sections from the spinal cord of cats even 20 days old (older animals have not been used), and sections of the hypoglossus, facial and oculomotor nuclei of 30 day old cats have been so stained. As a rule, the synaptic knobs in the cord can be studied in the 10-15 day old cat. It is a rather general belief that the knobs develop late, but the fact underlying this belief is that reduced silver methods fail to yield satisfactory stains at those ages. However, when synaptic junctions from animals at ages at which completed myelination begins to prevent obtaining a satisfactory Golgi stain are compared with synaptic junctions from young but fully developed or even adult animals, stained with the Golgi-Cox method, no essential difference is observed.

Cells *A* to *E* in Fig. 3 are motoneurons and cell *I* presumably is large internuncial. All of these cells are from the anterior horn of the lumbar cord of a 15-16 day old cat. In the original preparation they are stained a light orange color, while the fibers and knobs are stained black or a deep red. The number of stained fibers is small, and hence there is opportunity to follow each fiber and its branches throughout their entire trajectory within the 100 $\mu$  thick section.

From the majority of fibers near the group of motoneurons *A* to *E* only relatively short segments are included in the section; but there is a fiber 6 which has a relatively large segment and is seen to establish synaptic junctions with two motoneurons, *B* and *C*. Fiber 6 which also establishes synaptic junctions with dendrites is a branch of a slightly thicker fiber, which in turn is a collateral of another fiber of the anterolateral tract. The parent fiber, therefore, establishes connections with many motoneurons and internuncials—a well-known fact which does not require emphasis.

It will be noted that during its trajectory along cell *C*, fiber 6 gives off a series of branches, each one of which ends on cell *C* by means of one, two, or even a cluster of knobs. The total number of knobs is large, but it is remarkable that these knobs are not located in the immediate proximity of one another, being separated by spaces which are no doubt occupied by knobs belonging to other fibers. Fiber 6 then divides into two branches, 6 *a* and 6 *b*. Fiber 6 *a* has five knobs on the body of cell *B* and finally ends in an intercellular space having several small synaptic thickenings (*d*) obviously in contact with dendrites. Fiber 6 *b* establishes contacts presumably only with dendrites.

The connections of fiber 2 with cell *C* also are clearly seen in the preparation. Branch 2 *a* obviously establishes contacts only with dendrites, for no cell body can be located in that narrow intercellular space; but branch 2 *b*, after having formed some knobs *d* in contact with dendrites, has a trajectory parallel to the border of cell body *C*, in the course of which it gives off tiny branches terminated by knobs on cell body *C*. It will be observed that the second fibril before reaching *C* has two tiny thickenings which must necessarily be in contact with dendrites.

Another type of fiber having contacts with cell *C* is fiber 5, which ends with a cluster of knobs at the base of a large dendrite. In the case of cell *C* the orientation of the section is such that fibers 2 and 6 happen to be in the equa-

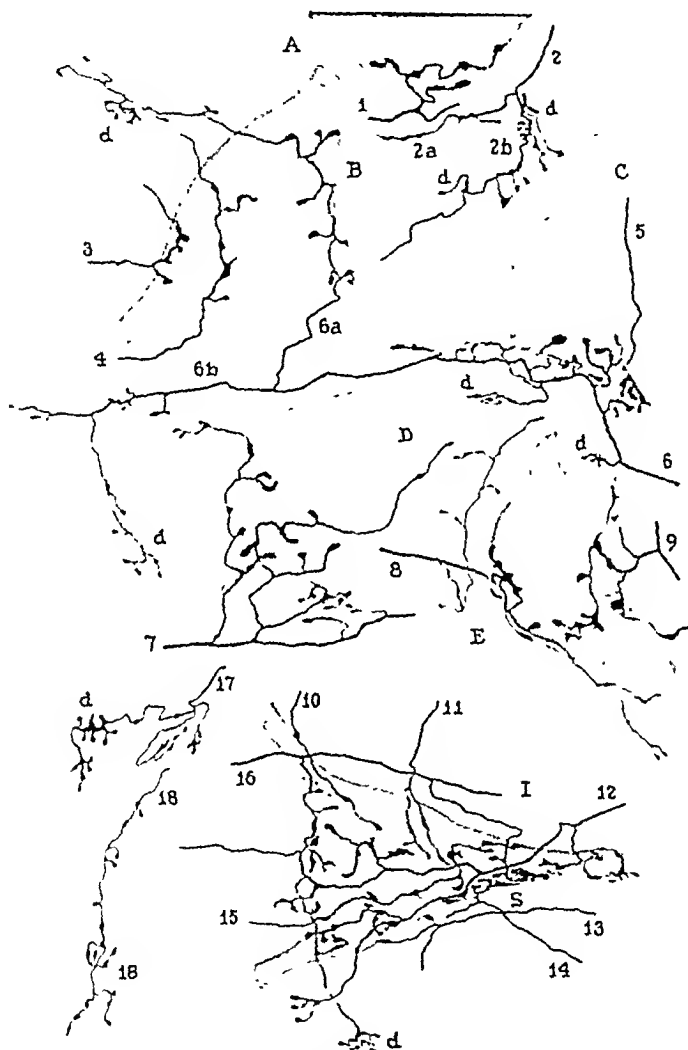


FIG. 3. Synapses on motoneurons (A to E) and on a large internuncial (I) of the spinal cord of a 15-16 day old cat. Silver-chromate method of Golgi. *d*, synaptic knobs in contact with dendrites.

torial plane of the cell body, so that the true relations of cell, fibers, and knobs can be observed. This relationship can still be seen, although but partially, in the case of fiber 7 and cell *D*. The knobs are in contact with the cell body,

but the fibrils connecting the knobs are not in contact with the cell. In the spaces left by the connecting fibrils and the cell, other fibers and tiny dendritic branches are located. In the case of cells A, B, and E, the stained synapses are located on the upper surface of the cell and for this reason the distances between the knobs formed by each fiber are better observed than in the other cells.

All these pictures are, of course, incomplete because only a few fibers were stained. The body of the cell is in fact always entirely covered with synaptic knobs belonging to many fibers, which form a continuous synaptic scale. It is obvious from the drawings of Fig. 3 that the synaptic scale is a mosaic of interlacing clusters of knobs, so that the activation of any discrete zone of the synaptic scale demands the conduction of impulses by several fibers. On the other hand, one fiber may help activate several different zones of the synaptic scale. An attempt to illustrate these facts in graphic form is made in the drawing of cell I taken from another section, and seven (10 to 16) of the stained fibers having knobs on the upper surface of the cell. It will be noted that while fibers 10, 11, 13 and 14 have but a small number of knobs, fibers 15 and especially 12 and 16 have numerous knobs distributed over a wide area of the cell body.

The motoneurons and large internuncials receive knobs from so many fibers that a complete picture is obtained only when the preparation is so heavily stained that the course of the individual fibers cannot be investigated in detail, but the small internuncials, especially in Cajal's intermediate nucleus, receive knobs from a relatively small number of fibrils, and therefore not infrequently one observes pictures such as that shown in Fig. 4, in which an important part of the synaptic scale is stained, while the cell itself has remained unstained.

Ten fibers ( $f_1$  to  $f_{10}$ ) having synaptic junctions with the upper surface of the cell body or dendrite  $d$ , or both, have been reproduced in the drawing. It can be seen that fibers  $f_1$  to  $f_{10}$  join dendrite  $d$  at some distance from the cell body, presumably at its point of bifurcation, the fibers follow the den-

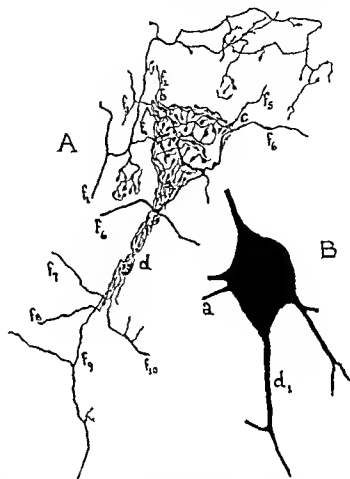


FIG. 4. A, synapses on a small internuncial neuron of the ventral ganglion of the acoustic nerve of a 20 day old cat. B, a cell of the same type. a, axon, b, c, d,  $d_1$ , dendrites,  $f_1$  to  $f_{10}$  fibers having synaptic junctions with cell A.

drite, having small thickenings in contact with it, and upon reaching the body form synaptic knobs in a manner similar to the fibers represented in Fig. 3. Fibers  $f_2$ ,  $f_3$ , and  $f_4$  reach the cell at the origin of dendrite  $b$ , and fibers  $f_5$  and  $f_6$  at the origin of dendrite  $c$ ; a collateral of fiber  $f_1$  reaches the cell body at a point which has no dendrite. It is obvious that if only a few more fibers had been stained, the synaptic scale would have been complete. Presumably it is almost complete at the level of dendrite  $d$ . While neighboring synaptic knobs are near each other, the distances being measured in fractions of  $\mu$ , they are still not in actual contact. Between them there seems to exist an amorphous substance, which by Golgi's method is at times stained a brownish red color. The nature of this substance is unknown; at present it cannot even be said whether or not it differs from the intercellular fluid. Neither can it be determined definitely whether it corresponds to the pericellular network described by Cajal, Golgi and others (cf. Cajal, 1935, Fig. 47). We can only state with certainty that between the synaptic knobs there is something which takes the Golgi stain in a manner different from the knobs themselves.

The drawing of Fig. 4 also illustrates another important fact. The continuous synaptic scale formed by interlacing clusters of knobs extends over the dendrites, but for only a short distance, usually up to the point where the dendrites branch out, and sometimes even for a shorter distance. This, with but few exceptions, is the general rule for all the types of neurons studied by the present author in the spinal cord, medulla, midbrain, thalamus, and cerebral cortex. The differences observed refer chiefly to the extension of the synaptic scale beyond the limits of the cell body, the size of the knobs, the homogeneity of the fibers contributing to the scale, etc.

For the synaptic junctions of dendrites the description must be made in general terms, for the reason that a detailed analysis has not yet been completed. On the other hand, not all dendrites are alike, and there are important differences between dendrites of cells of various types, and even between the dendrites of one cell.

A general description may be attempted in the following terms. In the intercellular spaces, *i.e.*, in the spaces between cell bodies, there are besides glia cells, blood vessels, and myelinated fibers, two plexuses—one formed by dendritic branches, and the other by unmyelinated fibers which carry numerous synaptic thickenings. Fibers 17 and 18 of Fig. 3 are typical fibers of the plexus in the anterior horn of the cord, and so are the thin collateral branches of the other fibers in the same figure. Accurate representations of the dendritic plexuses have been given in other publications (cf. 1938c, Fig. 1; 1933, Fig. 12). Both dendritic and fibrillar plexuses have numerous synaptic junctions. It can be said that a dendrite while crossing the fibrillar plexus establishes junctions with fibrils of most varied origin, and that a fibril while crossing the dendritic plexus makes junctions with numerous dendrites of various types of cells. An attempt to illustrate graphically the relation between the two plexuses is made in the diagram of Fig. 5.

In parts of the nervous system where the arrangement of the dendritic

and fibrillar plexuses is systematic, as for example in the cerebral cortex and the tuberculum acusticum, it is possible to establish the existence of an orderly regional arrangement of synapses on the various dendrites (1933, 1934); but in the anterior horn of the spinal cord and the motor nuclei of the cranial nerves, an analysis of the dendritic connections is made difficult by the apparent lack of regularity.

There are motoneurons with dendrites distributed exclusively within the limits of the motor pool, and consequently the dendrites have connections with fibers also contributing to the synaptic scale on the cell bodies. But other motoneurons have dendrites extending far beyond the limits of the motor pool, and these have connections with the fibrillar plexus of internuncial pools. There are internuncial cells located in the immediate proximity of the motor pool, with no dendrite penetrating the latter; but there are also internuncial cells, sometimes with the bodies at considerable distances from the motor pool, which send dendrites into the pool, where they establish contacts with the fibrillar plexus of the latter. It is obvious that for the dendrites the same general rule holds as for the cell bodies, namely that activation of all the synapses in any discrete length of a dendrite demands the simultaneous conduction of impulses by several fibers of the plexus.

#### DISCUSSION

Threshold stimulation of a motoneuron does not require the activation of all the synaptic knobs, for the stimulation may have all gradations of intensity, from subliminal to supramaximal, *i.e.*, capable of firing a refractory neuron. On the other hand, the stimulation may be produced by the activation of different sets of knobs. This conclusion may be reached from a study of the experiments shown in Figs. 1 and 2, but more direct proof has been obtained in experiments in which it was shown that the same motoneurons may respond either to an *f* volley or to one of internuncial impulses (1938c, Figs. 3, 4 and 5). Increase in the number of knobs active constitutes an increase in the strength of stimulation; but the number of active knobs is not the only determining factor, because it has been shown that a small volley of *f* impulses may set up a response, while a large *f* volley may fail to do so. In view of the anatomical data, the most reasonable explanation seems to be that stimulation of the motoneuron demands the activation of all the synapses

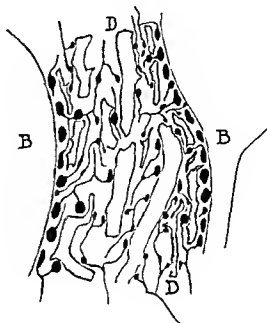


FIG. 5. Diagrammatic representation of the articulation of the dendritic and fibrillar plexuses in the gray matter of the spinal cord. Cell bodies (B) and dendrites (D) in gray; fibrils and synaptic knobs in black.



on a discrete zone of the motoneuron, a condition that in the present experiments cannot be fulfilled by the activation of *f* or *i* fibers alone, undoubtedly because the synapses of each kind are scattered over the neuron. For example, let it be assumed that in Fig. 3, *I*, fibers 10, 11, 12, 13, 15 and 16 are *f* fibres. Stimulation of any number of these fibers will fail to activate all the synapses or any discrete zone of the soma; but if to the *f* volley an impulse through fiber 14 be added, all the synapses on the zone marked with *s* will be activated and the neuron will fire. Obviously, if fiber 14 conducts an impulse, there is no need for all the other fibers to be activated; threshold stimulation will be obtained if fibers 12 and 16 only are active. Obviously, other sets of fibers will cause the impulse to start at another zone of the soma.

This explanation, which is supported also by the first two lines of evidence mentioned in the introduction, applies as well in the case where the effective knobs are located on the cell body as in that of knobs located on dendritic branches. The latter, for example, is true of the olfactory bulb, because the olfactory fibers establish synapses with the dendritic bushels of the mitral cells. However, much work must still be done before the role of the various types of dendrites is fully understood.

The fact that liminal stimulation is obtained by the activation of a discrete zone of the soma does not indicate that the subliminal disturbance produced underneath any knob does not spread for a certain distance. The fact that summation takes place demonstrates conclusively that it does spread, at least to the next knob (Eccles and Sherrington, 1931). But the available evidence does not provide us with sufficient data to estimate the amount of the spread. The only permissible assumption is that effective summation demands the activation of knobs located at a distance from each other which is shorter than in the case of knobs belonging to one fiber.

An interesting conclusion to be drawn from this discussion is that the *f* and *i* synapses, which during ether narcosis are activated by shocks delivered to the posterior longitudinal bundle, are scattered over the soma of the motoneuron, so that an *f* or an *i* volley in isolation cannot result in the activation of all the synapses on any discrete zone of the motoneurons, but the *f* synapses must be so concentrated on some *i* cells that an *f* volley fires them. This conclusion is in agreement with known facts.

From the anatomy of the oculomotor preparation (cf. 1938c, Figs. 1 and 2) it follows that the *F* shock activates the posterior longitudinal bundle and adjacent pathways, which after giving collaterals in the oculomotor nuclei, end in the internuncial nuclei containing chiefly small neurons. The synaptic scales on these neurons are of the type illustrated in Fig. 4 and may be activated, at least in large zones, by the volley of *f* impulses. Thus it could be assumed beforehand that these neurons would respond to any *f* volley which is sufficiently large. Similarly, it could have been predicted that a volley of impulses conducted by the axons of these cells would in isolation be insufficient to fire motoneurons, for as these axons are thin, they can have but few contacts with any neuron. Neither is there difficulty in explaining why under

ether narcosis facilitation is of short duration. The large neurons of the internuncial nuclei having synaptic scales of heterogeneous origin are not activated by the  $f$  impulses. Therefore, long closed chains of neurons do not come into play, and facilitation ceases as soon as the impulses have crossed all the synapses in the open delay paths, which in the case of the experiments recorded in Figs. 1 and 2 means four or five internuncial synapses. But what was rather astonishing was to find the  $f$  volley in isolation incapable of firing motoneurons, for the powerful branches of the posterior longitudinal bundle form extensive arborizations in the motor nucleus. Attempts to analyze the distribution of the  $f$  synapses in the oculomotor nucleus have as yet failed, for the anatomical conditions present are unfavorable for detailed study. But in the hypoglossus nucleus it has in fact been found that each one of the long bundles sending collaterals into this nucleus has a certain type of terminal fibers in the nucleus, and that the axons of the small internuncials located in the neighborhood of the motor pool again have their specific distributions. It is, therefore, likely that the  $f$  synapses on the ocular motoneurons are systematically arranged on strategic zones of the neurons, so that only the summation of  $f$  impulses with impulses carried by other pathways is possible. It will be remembered that if a shock is delivered to the internuncial nuclei in front of the oculomotor nucleus, so that  $f$  and  $i$  fibers are stimulated simultaneously, ether narcosis does not prevent some motoneurons from responding; and that if a background of internuncial activity is present, the  $f$  volley may fire the entire population of the motor pool.

#### SUMMARY

Although the threshold stimulation of motoneurons requires that several impulses be delivered simultaneously at their synapses, not all the fibers contributing to the synaptic scale need be active. Experimental results demonstrate that while the activation of a large number of synapses may remain ineffective, activation of a limited number of those synapses, effected simultaneously with the stimulation of other fibers, results in the setting up of a response. Furthermore, it is shown that effective stimulation of motoneurons may be produced by the activation of different groups of fibers.

Anatomical studies have revealed that the synaptic scale of the motoneurons consists of interlacing clusters of knobs belonging to a large number of fibers and that the synaptic terminals of each fiber are located at some distance from one another. The activation of all the synaptic knobs at any discrete zone of the soma demands that several fibers be conducting impulses. It is obvious that different groups of fibers will cause stimulation at different zones of the soma.

It is concluded, therefore, that the setting up of a new impulse by the motoneuron results from a localized process taking place underneath a dense group of active synaptic knobs. Subliminal responses must be propagated decrementally but the information available is insufficient to estimate the amount and rate of the spread.

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# ANALYSIS OF THE ACTIVITY OF THE CHAINS OF INTERNUNCIAL NEURONS

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## INTRODUCTION

ALL THE neurons in the central nervous system are reciprocally connected by numerous pathways, some having great and others lesser degrees of complexity. This wealth of connections is due not only to the high number of neurons and pathways, but also to the branching of the axons and their collaterals and to the overlapping of the fields of distribution of the branches of the different axons. The number and complexity of central pathways are best described by saying that, with but few exceptions, at least one pathway can be found connecting any two central neurons in a manner so that an impulse may be conducted from one to the other neuron in the direction of axon-synapse-body or dendrite-axon. Obviously many of these complicated paths are physiologically impassable, because the impulses sooner or later fail to reach the threshold of an intervening neuron, but others actually do play an important role in the physiology of the central nervous system. This question was discussed at some length in previous papers (1928, 1933c, 1934a) in which the literature of the subject has been reviewed. Recent advances in the knowledge of the physiology of the synapse (reviewed by Eccles, 1936b, 1937a, b; Bremer and Kleyntjens, 1937; Fulton, 1938; Lorente de Nó, 1938b, c) make it possible to analyze in greater detail the physiological significance of the arrangement of the neurons in synaptic chains.

The interest of the analysis consists in that it is possible to reduce the actual anatomical complexity of the nerve centers to simple diagrams suitable for theoretical arguments. Within the extreme variety of connections established by any one neuron with neurons of the same or of distant pools there is a systematic repetition of two fundamental types of circuit, which may be called the multiple (Fig. 2, *M*) and the closed chain of neurons (Fig. 2, *C*). The chains may be longer or shorter, they may contain a larger or smaller number of parallel branches, but in every case they remain essentially the same. Thus it comes about that the cerebellum as an organ is, from the point of view of elementary physiology, a giant chain of internuncial neurons, superimposed upon the reflex arcs in the spinal cord and the medulla (1924). Its activity consists in regulating the transmission of impulses through the shorter arcs. Similarly, the complex anatomical mechanisms found in the reticular substance of the medulla, pons, and midbrain can be reduced to chains superimposed upon the shorter arcs, and it is understandable that if the short arcs have been destroyed through suitable operation, motor reactions can be elicited through the longer chains of the reticular formation (1928; Spiegel,

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1929). Nor is it difficult to account for the fact that the internuncial system in the reticular formation may be the locus where inhibition of motor responses is produced (1928, 1931; cf. Sherrington, 1934).

An analysis of the activity of the chains of internuncial neurons has been made in the oculomotor preparation (1935a) which affords an opportunity of stimulating large fiber tracts known to establish synaptic connections with the ocular motoneurons. Diagrammatic representations of the preparation have been given in previous reports (1935a, e) but additional details are needed.

Since in physiological literature the internuncial system has not received the attention that its anatomical importance justifies, it is necessary first to reproduce an actual anatomical picture in which the relative number of motor and internuncial neurons is immediately seen. Fig. 1 reproduces part of a section through the medulla and midbrain of an adult mouse stained after Golgi-Cox. It contains the oculomotor nuclei (VI, IV, and III) and a few of the nuclei of the system of correlation located in the reticular formation of pons and midbrain. In it, it is patent that the motoneurons are outnumbered many times by the internuncial cells\* of the reticular formation, which regulate their discharge.

Actual reproductions of pathways connecting these neurons among themselves and with the motoneurons have been published by a number of authors (Cajal, 1909, Fig. 361; 1911, Figs. 151, 155, 156, 157; Whitaker and Alexander, 1932; Lorente de Nó, 1924, 1933a, c, e, etc.). The diagram in Fig. 2 has been constructed on the basis of these data.

The diagram emphasizes several important points: (1) Next to pathways (1, 2, 9, 10, 11) having direct connections with the motoneurons there are pathways (3, 4, 5, 7, 8, 12) that end in the reticular formation without direct connections with the motoneurons. Therefore the impulses which they carry can reach the motoneurons only after having crossed through an additional internuncial neuron. (2) All the pathways that establish connection with the motoneurons also have synapses with cells of the reticular formation, so that

\* The name internuncial neuron . . . . . neuron in the central nervous system, with the exception of the classification of the cells in each argument is considered. Impulses are conducted into a pool of neurons by afferent fibers and out of the pool by efferent fibers, which are axons of some cells of the pool. The cells of origin of the efferent fibers transmit the effect of the activity of the pool and may be called "effector neurons"; all the other nerve cells in the pool are internuncial neurons. Consequently a cell may be called effector or internuncial according to the problem being studied. In the present case the axons of cells in the vestibular and reticular nuclei that run directly to the motor . . . . . not called internuncials because they are made . . . . . the shocks were delivered to the vestibular ne . . . . . he internuncials of the second, third, etc. order, according to the number of synapses crossed by the vestibular impulses on their way to the motor nucleus.

The concept . . . . . ally different from the concept of the intercalary cell . . . . . cause, as Cajal long ago (1911, p. 590) pointed out, . . . . . to which v. Monakow referred are not intercalated h . . . . . cells with long axis cylinder; they form a collateral chain superimposed upon the articulation of afferent fiber-cell with long axon.

whenever an impulse is delivered to a motoneuron, impulses also arrive at internuncial cells. (3) The internuncial neurons are arranged in chains of two types: *M* (principle of plurality of connections, 1933c, p. 248) and *C* (principle of reciprocity of connections, 1933c, p. 249), which, with but few exceptions, are also found in every part of the central nervous system.

It is an immediate consequence of the anatomy of the preparation that shocks through electrodes *F* or *Col* by stimulating axons or cells set up a volley of impulses, called *f* or *c* according to the electrodes used, which, after conduction, is delivered to the motoneurons. Furthermore the *f* or *c* volley is also

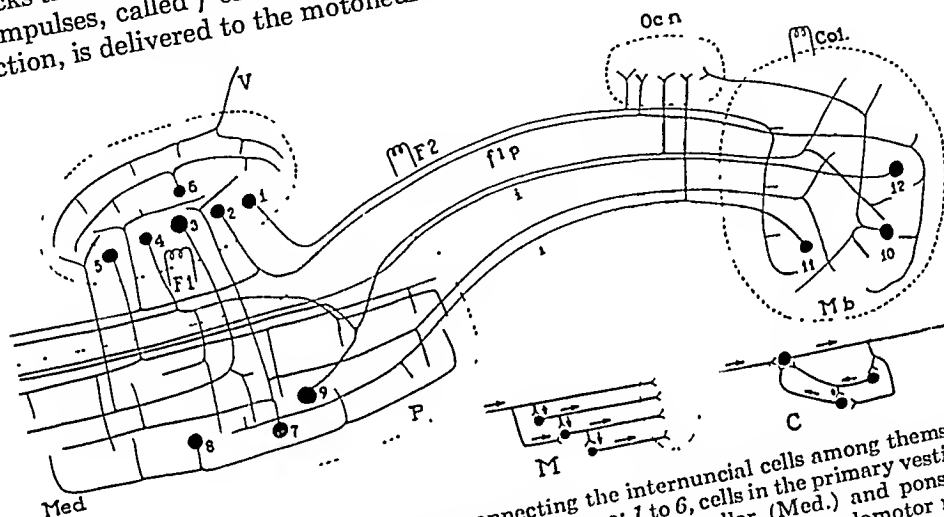


FIG. 2. Diagram of the pathways connecting the internuncial cells among themselves and with the ocular motoneurons. V, vestibular nerve; 1 to 6, cells in the primary vestibular nuclei; 7, 8, 9, cells in the reticular formation in the medullar (Med.) and pons (P.); 10, 11, 12, cells in the reticular nuclei in the midbrain (M.b.); Oc.n., oculomotor nuclei; f.l.p., fasciculus longitudinalis posterior and similar pathways; i, internuncial pathways; F1, F2 and Col., position of the stimulating electrodes. The diagrams below indicate the two types of chains formed by internuncial cells; *M*, multiple and *C*, closed chain.

delivered to internuncial cells, which may respond and fire new volleys of impulses, necessarily delivered, at least in part, again to the motoneurons. In previous reports (1935a, to e) attention was paid especially to the effect of the *f* or *c* impulses. Here the effects of the internuncial impulses will be examined in greater detail.

#### TECHNIQUE

The experiments here presented have been made on the oculomotor preparation of the rabbit as previously described (1935a, e), the only difference being that in some experiments the responses were recorded from the trochlear nerve. The stimulating *F* electrodes on the floor of the fourth ventricle were placed in some experiments on the caudal part of the vestibular nuclei (position F1, Fig. 2), and in other experiments at the level of the abducens nucleus (position F2, Fig. 2). With electrodes in position F1, the number of impulses directly conducted to the motoneurons (*f*, Fig. 3) is smaller than with the electrodes in position F2, so that the response is established chiefly through the internuncial system. The cathode of the *C* electrodes introduced in the anterior colliculus was placed approximately as indicated in Fig. 2, Col.

## RESULTS

The records reproduced in Fig. 3 were obtained under conditions favoring internuncial discharge. The head of the rabbit was tilted some  $40^\circ$  upwards, so that there was a considerable tonic labyrinthine innervation of the superior oblique muscle, which revealed itself by small irregular waves of the electrogram of the trochlear nerve. The impulses started by a shock through electrodes F1 could thus summate with the constant stream of labyrinthine impulses maintaining the tonus of the superior oblique muscle. Single shocks of progressively increasing strength were delivered at two-second intervals.

For records 1 and 2 (Fig. 3) the stimulus was barely at threshold and there is an indication of response only in record 1; but in records 3 and 4 the response was rather large. As in 1, it consisted in a re-enforcement of the tonic waves lasting for some 4-5 msec. The response increased when the shock was strengthened (5, 6, 7, 8), with the peculiarity that the largest potential waves often appeared at about the middle part of the response. Further strengthening of the shock (9, 10, 11) to maximal (12) and hypermaximal value (13, 14) caused additional increase of the response. However, the increase of the early potential waves was not accompanied by increase of the late ones; on the contrary, the latest waves disappeared and the response became shorter (cf. records 13 and 14 with 6, 7 and 8).

The type of response shown in records 1 to 8 of Fig. 3 is one that might be expected. The stimulating shock created a volley of impulses partly delivered to the motoneurons and partly to internuncial cells; some motoneurons responded to the volley and their impulses reached the recording electrodes. Some internuncials also fired and caused other motoneurons and internuncials to respond. Likewise, this second volley of internuncial impulses stimulated other motoneurons and internuncials to discharge impulses into their axons, etc. The process was completed when the

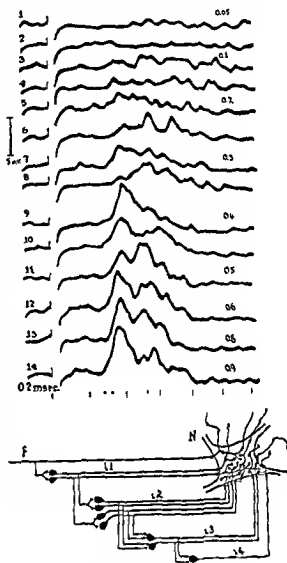


FIG 3. Oculomotor preparation of the rabbit; responses recorded from the trochlear nerve. Stimulating electrodes in position F1 (Fig. 2), (2-2-36). The numbers on the right hand side of the records indicate the strength of the shock in potentiometric units. The diagram below indicates the temporal and spatial distribution of impulses arrived at the motoneuron N after a shock is delivered to fiber f; i1, i2, i3, i4, internuncial paths. Passage of a synapse means a delay of about 0.6 msec. Note that each fiber has several synaptic knobs on the neuron, an arrangement increasing the possibility of spatial summation.



internuncial volleys failed to reach threshold value for the next neurons. Since the average synaptic delay of internuncial cells is about 0.7 msec., it is fair to assume that responses such as those shown in records 7 and 8 had involved passage of the impulses through four or five internuncial neurons.

What *a priori* could not be expected is that strengthening of the shock, *i.e.*, increase of the size of the *f* volley, would cause the response to lose the late waves (records 9 to 14). This has only one explanation, namely, that the motoneurons, which in weak responses fired upon arrival of late internuncial volleys, in response to strong shocks fired when stimulated either by the impulses of the initial (*f*) volley or by the early internuncial volleys, and they could not fire again for the remainder of the response. The late internuncial volleys were lost because they were delivered to refractory neurons.

This result is expressed in graphic form in the diagram at the bottom of Fig. 3. The fiber marked *f* belongs to the posterior longitudinal bundle and is supposed to reach a motoneuron eventually engaged in the response to the *F* shocks. *i.1.*, *i.2.*, *i.3.*, and *i.4.* are those few internuncial pathways which are crossed by the impulses in their way to the motoneurons. It is seen in the diagram that if the motoneuron (*N.*) does not respond to the *f* impulses, it may respond to the internuncial impulses after a latency equal to one, or to the sum of several synaptic delays; but if it is fired by the *f* impulses it will not reappear in the response as long as the *i* impulses find it in a refractory state.

Since even the strongest responses (12 to 14) contained only a small fraction, *i.e.*, scarcely one-third, of the total cell population of the motor nucleus, the diagram also illustrates the fact that the internuncial volleys were delivered in great density again and again to a small number of neurons, or in other words, that despite the many possible channels for conduction into branches (Figs. 1 and 2) the impulses remained confined within a few selected channels, so that the majority of the neurons of the motor pool received only subthreshold stimuli. Using a term introduced by the Oxford school (Cooper, Denny-Brown, and Sherrington, 1926) it may be said that during activity the internuncial and motor pools become *fractionated* into active and inactive groups, part of the latter group constituting a *subliminal fringe* (Denny-Brown and Sherrington, 1928), the activation of which demands stimulation by another set of pathways. In the particular case under consideration the fractionation was already established by the tonic labyrinthine innervation in which, as in other tonic innervations (*cf.* Denny-Brown, 1929; Adrian and Bronk, 1929), a small number of motoneurons are continuously engaged. Apparently the shock delivered to the posterior longitudinal bundle and other secondary vestibular paths temporarily altered the fractionation by causing some motoneurons of the subliminal fringe to enter into the active group. But still the additional impulses were unable to reach the threshold of neurons that were not already in the subliminal fringe. As a result, when a large number of the facilitated motoneurons responded (Fig. 3, 12 to 14), the later internuncial volleys became ineffective.

The diagram of Fig. 3 deserves especial consideration because it repre-

sents the relatively simple type of chains of neurons in which the internuncial system becomes fractionated during transmission of impulses. It has been substantiated by a number of other experiments. That the impulses of successive internuncial volleys actually are delivered repeatedly in great numbers to a small number of motoneurons is demonstrated in a most conclusive manner by the records in Fig. 4 obtained by successive delivery of two F1 shocks. Either shock alone (records 1 and 2) set up a response as in Fig. 3, 10 and 12 respectively. When both shocks were delivered in succession at intervals of 0.5 msec. or more, the response to the second shock increased considerably, but only in its early wave; the late waves were considerably reduced even when the facilitation was greatest (record 5). At that moment the response to the testing shock became a practically synchronous spike somewhat less than half the maximal nerve spike. As there can be no doubt that the testing *f* volley was followed by successive volleys of internuncial impulses, the lack of late waves in the facilitated response demonstrates that the *i* impulses were delivered to the same motoneurons that had responded to the *f* volley.

Records 7 to 10 correlate the duration of the period of facilitation and the duration of the response to the conditioning shock. As shown by record 8, the total duration of the conditioning response was about 4–5 msec., which also was the duration of the period of facilitation. In record 7, where the interval between shocks was 3.52 msec., the facilitation was still great; but in record 10, where the interval was 5.3 msec., there was no appreciable increase of the testing response. Evidently in the oculomotor preparation the increase in strength of stimulation necessary to bring motoneurons of the subliminal fringe into the active group is so small (cf. 1938c) that unless some motoneurons are engaged in the response, the extension of the subliminal fringe is negligible.

Since the period of the summation of impulses delivered at different synapses is extremely short (1935c, d; for sympathetic ganglion cells see Eccles, 1937b), there can be no doubt that the height of the initial wave in the facilitated response (records 3 to 7) measures the number of inter-

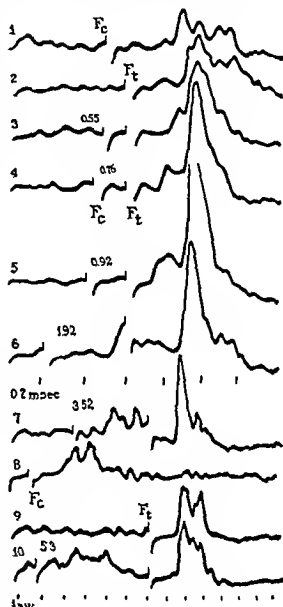


FIG. 4. From the same experiment as in Fig. 3. Two F1 shocks are delivered at the intervals indicated on the records 1 and 8 reproduce the conditioning and 2 and 9 the testing responses in isolation.

nuncial impulses entering the motor nucleus at different moments after delivery of the conditioning F shock. The testing volley of  $f$  impulses was of course constant, because the testing shock was maximal, and consequently the number of responding motoneurons was roughly proportional to the number of  $i$  impulses arriving at the motor nucleus simultaneously with the  $f$  impulses. The temporal course of facilitation demonstrates that the internuncial volleys had more or less the densities indicated in the diagram in Fig. 3, the largest volleys being  $i_1$  and  $i_2$  after the impulses had crossed through one or two internuncial neurons.

The records in Fig. 5 obtained in another experiment also are very demonstrative. In this experiment the electrodes were placed in position F2 (Fig. 2), with the result that the initial  $f$  volley was large enough to cause the appearance of a considerable  $f$  wave, while the waves of internuncial origin were small (Fig. 5, 1, 2). Nevertheless, it could be demonstrated that the  $f$  volley was followed by powerful  $i$  volleys which remained ineffective because they were delivered almost exclusively to those motoneurons that had been made refractory by their response to the  $f$  impulses. The experiment was based on the following argument (1936, Fig. 4; cf. Eccles, 1931, p. 582). An antidromic shock was delivered to the motor nerve in order to create refractoriness of the motoneurons, and at different moments during the period of recovery an F response was elicited. The impulses of the initial  $f$  volley reached the motoneurons while their threshold was still high and failed to elicit responses, but the  $i$  volleys, which arrived at the motor pool after delays of 0.6 msec. or more, found the motoneurons at a more advanced state of recovery and were able to set up responses. By properly choosing the interval between the antidromic and the F shocks it was possible to obtain F responses

in which the  $f$  wave was small, while the  $i$  waves were large (Fig. 5, 9, 10); as the rate of recovery of the motoneurons is rather slow (1935c; Lorente de Nó and Graham, 1938), it must be concluded that the  $i$  volleys were almost as

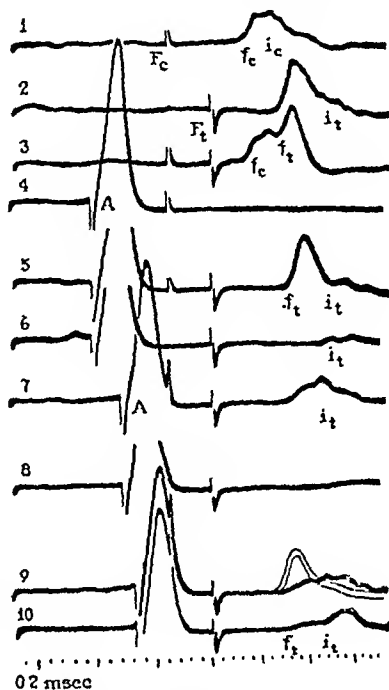


FIG. 5. Oculomotor preparation; responses recorded from the trochlear nerve. Stimulating electrodes in position F2 (Fig. 1) (2-5-36).  $F_c$  and  $F_t$ , conditioning and testing F shocks;  $i_c$  and  $i_t$ , responses to internuncial impulses; A, maximal antidromic shock and its response. In record 9 the unconditioned  $f_i$  response has been reproduced (in light tracing) on the conditioned one. Records 1 to 6 were obtained at slightly higher amplification than records 7 to 10 (cf. height of the A responses).

strong as the *f* volley, although in strong unconditioned *F* responses (Fig. 5, 2) the *i* waves were practically absent.

The actual experiment is illustrated by the records shown in Fig. 5. Two *F*<sub>2</sub> (Fig. 2) shocks (*F*<sub>0</sub> and *F*<sub>1</sub>) were delivered in succession at the constant interval of 0.8 msec., and a maximal antidromic shock was delivered at three different intervals (1.30, 0.8, and 0.6 msec.) before the first *F*<sub>2</sub> shock. Both the conditioning (Fig. 5, record 1) and the testing shock (record 2) set up responses with a large *f* wave followed by small *i* waves; but in a similar manner as in the experiment of Fig. 4 when the *F* shocks were delivered in succession, the *i* waves in the response to the testing shock disappeared (record 3).

The maximal antidromic shock when delivered 1.30 msec. before *F*<sub>0</sub> prevented any response to this shock (record 4); but when *F*<sub>0</sub> was followed by *F*<sub>1</sub>, the response to the latter contained a large *f* wave (with slightly lengthened latency) and, in striking contrast with the response in record 3, also well marked internuncial waves (*i*<sub>1</sub>). When *F*<sub>0</sub> was omitted, the response to *F*<sub>1</sub> (record 6) contained only *i* waves.

When the antidromic shock was approached to the *F*<sub>1</sub> shock (record 7) the response to *F*<sub>1</sub> changed in a spectacular manner; the early *f*<sub>1</sub> wave decreased, while the internuncial waves increased considerably. If *F*<sub>0</sub> was omitted no response was obtained (record 8). Further decrease of the interval between the antidromic and the *F*<sub>0</sub> shock to 0.6 msec. resulted in a further decrease of the *f*<sub>1</sub> wave, without reduction—there rather was an increase—of the internuncial waves (records 9 and 10).

The fractionation of the internuncial and motor pools is maintained even in the case of repetitive stimulation creating strong activity. In the experiment illustrated by the records in Fig. 6 a rhythmic series of shocks was delivered through C electrodes (Fig. 2, Col). The responses were recorded from the left trochlear nerve and the C cathode was placed in the reticular formation in front of the left oculomotor nucleus. Since the nucleus of the left trochlear nerve is located on the right side, the shock did not stimulate trochlear motoneurons, but stimulated trochlear axons shortly after they had crossed the middle line. This response is labeled *n* on records 13, 14, 17. Synaptic responses of trochlear motoneurons, labeled *s*, had of course a longer latency.

Single shocks of any strength or tetanic stimulation at low frequency failed to set up synaptic responses, but when the frequency of the series was raised (1 to 9) synaptic responses appeared after a period of recruitment including never less than three shocks; after a further period of increase, the responses remained at rather constant level, roughly proportional to the frequency of the series.

The recruitment was obviously attributable to the same process which underlies the facilitation of responses of motoneurons to two shocks in succession (1935c, e). The first shock created impulses which lowered the threshold of some internuncial cells to synaptic and electrical stimuli; therefore the second shock was able to stimulate a larger number of internuncials and create

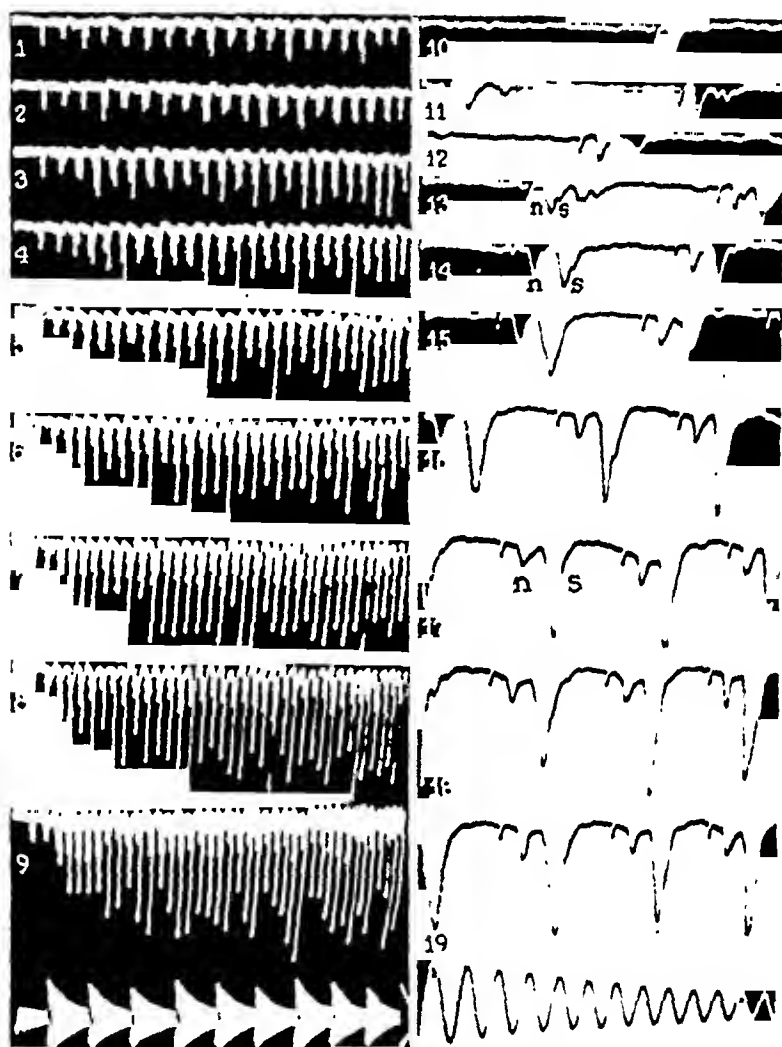


FIG. 6. Oculomotor preparation; responses recorded from the trochlear nerve. Electrodes in position Col. (Fig. 2) (3-9-36). Tetanic stimulation. The records on the right side were obtained at higher sweep speed than those on the left. Time (1/60 and 1/1000 sec.) below each series of records. Note that downwards deflection indicates negativity at the active electrode. *n*, response of directly stimulated trochlear fibers; *s*, synaptic responses.

a greater facilitation of the third shock, etc. The process was cumulative and soon the internuncial bombardment became large enough to enable the motoneurons to respond to the impulses of the direct volley (*c*) of impulses started by each C shock in internuncial axons or cells (cf. discussion, *e*). However, the recruitment did not progress beyond a certain limit; here as in the case of reflex responses fractionation took place. In fact the responses in the

experiments of Fig. 6 did not include more than a third of the total number of cells of the motor pool.

An analysis of the response can be made on the basis of records 10 to 19 which contain the middle part of responses similar to those on the left side, photographed at higher sweep speed.

At frequencies of less than 100 per second there was no synaptic response following the *n* wave (10), but at the frequency of 120 per second (11) the *n* wave began to be followed by an asynchronous synaptic response including several wavelets. The same type of response was observed at frequencies up to 145 per second (15). In terms of the diagram in Fig. 3 this type of response indicates that the initial volley of *c*\* impulses was sufficient to reach the threshold of only a small number of motoneurons, while the following *i*<sub>1</sub>, *i*<sub>2</sub>, etc., volleys were able to fire a larger number. It is important to note that in record 13 the synaptic response, despite its small size, appeared after the minimal synaptic delay (cf. 1938b).

Increase of the frequency of the series resulted not only in an increase but also in a shortening of the duration of the synaptic response, which soon (17 to 19) became a synchronous spike. Evidently the *c* impulses set up by each C shock met at the motoneurons a large internuncial volley due to the preceding shock and were capable of firing a large number of motoneurons. The following *i* volleys, being delivered with great density only to refractory neurons, failed to set up new responses. Here again, as in the previously studied, cases despite the great internuncial activity the *i* impulses arrived in large numbers only at a discrete number of neurons.

The fractionation of the motor nucleus was accentuated by the progressive increase of threshold (summation of subnormality) of the neurons engaged in tetanic activity. Although there is no conclusive proof, it is most likely that the motoneurons were following each shock of the series. As indicated by records 10 to 15, at low frequencies some motoneurons, obviously those near the subliminal fringe, alternated; but at higher frequencies the motoneurons must have followed every shock, otherwise some of them would have responded after the minimal synaptic delay, as in record 13, and not after the maximal delay, as in records 17 to 19. The frequency of the series necessary for effective recruitment was well above the critical one for summation of subnormality, *i.e.*, about 100 (cf. Lorente de Nó and Graham, 1938) so that once the motoneurons responded to two shocks in succession, their threshold became so high that they could respond again only to very strong stimuli, which apparently were created only by the coincidence of a *c* and an *i* volley. In the absence of *c* volleys, the *i* volleys would have been subliminal for any of the motoneurons engaged in the response. And in fact it is consistently found in experiments of this type that, despite the strong internuncial activity

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\* The volley of impulses set up by direct stimulation of axons or somata of internuncial neurons is called *f* or *c* according to the position of the stimulating electrodes (*F* or *Col.* Fig. 2). Later volleys which cross through one or more internuncial synapses are always called *i*.

created by the tetanus, after the end of the series of shocks the electrogram of the nerve, or muscle, showed a silent period of some 15 to 20 msec. duration, followed by a long-lasting tonic discharge (Fig. 9, 5, 13).

Experiments such as that illustrated by the records of Fig. 4 make the assumption likely that facilitation ends when the internuncial bombardment ceases. However, this demands careful consideration, because according to the observations of Eccles (1936a, b, 1937b), subliminal stimulation of the ganglion cell after the period of effective summation of impulses arriving at different synapses—called by Eccles “period of summation of detonator responses,” produces a long-lasting state of lowered threshold (Eccles’ *c.e.s.*). The fact must also be considered that the duration of the period of effective summation has been determined by studying the interaction of only two volleys of impulses, and it is thinkable that continued bombardment may lead to different results because it might produce a cumulative change in the motoneuron.

With ocular motoneurons it has as yet been impossible to demonstrate the existence of an enduring effect of subliminal impulses comparable to Eccles’ second phase of facilitation (*c.e.s.*), perhaps because in the cases studied internuncial bombardment and facilitation were inseparable. An instructive experiment will be mentioned here.

The series of records in Fig. 7 illustrate one type of interaction of F and C shocks. In isolation the F shock (3, 5, 18) caused the appearance of a response as shown in Fig. 3; the tonic discharge down the trochlear nerve was increased during a period of several msec. The C shock, however, caused a response composed of an almost synchronous spike potential followed by a silent period of several msec., during which the tonic discharge ceased (1, 2, 7, 21).

The F and the C shocks may have in part stimulated the same fibers, but there can be no doubt that they also stimulated different internuncial axons, because when delivered at simultaneity (22) more neurons responded than when either shock was delivered in isolation. When the F preceded the C shock, the response to the latter was facilitated (4 to 12), the period of facilitation lasting as in Fig. 4 through the period of increased tonic activity which followed the initial *f* discharge.

The results were different when the C preceded the F shock. At an interval of 0.2 msec. (20) the F response was greatly reduced even in its early wave, and it was practically abolished at an interval of 0.49 msec. (19). At greater intervals (17, 16, 15, 14, 13) the F response was totally abolished, as was the case also when the C response included only a small number of motoneurons (15). The F response began to reappear at an interval of about 4 msec. between shocks, and up to the last interval studied (5 msec.) it did not show signs of being facilitated.

The effect stated cannot be ascribed to the presence of some “inhibitory” impulses in the C volley, because when the F and the C shocks were delivered simultaneously (22) there was a marked summation. The assumption of “inhibitory” impulses in later internuncial volleys following the initial *c* volley also would be in conflict with the results of the experiment shown in Fig. 6

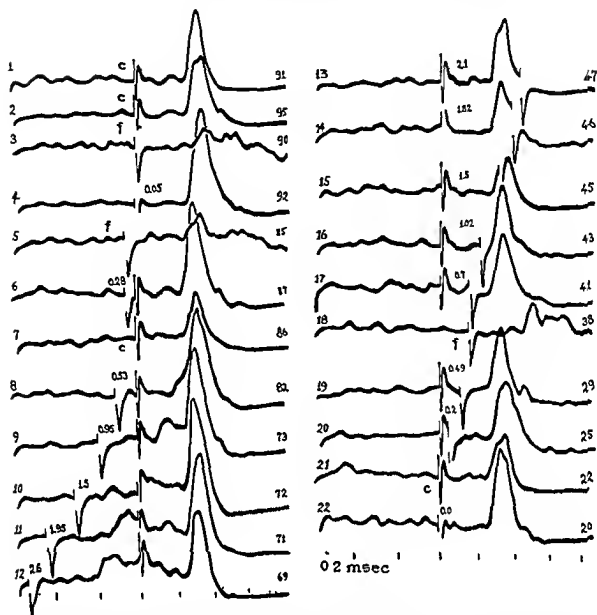


FIG. 7. Oculomotor preparation, responses recorded from the trochlear nerve. Two stimulating electrodes in positions F1 and Col (Fig. 2) respectively (same experiment as in Figs. 3 and 4). The responses to the C and F shocks in isolation have been reproduced in records 1, 2, 3, 5, 7, 18, and 21. There was a certain variation of height of the C response due to the discontinuous character of the tonic labyrinthine innervation, the response being of course larger when the c impulses happened to coincide with a large internuncial volley. Record 1 reproduces the largest observed response to a C shock in isolation. The numbers of the right hand side of the records indicate the order in which they were obtained, between each two consecutive records there was an interval of two seconds. For records 4 to 12 the F shock preceded the C shock at the intervals indicated in msec. on the records. For records 13 to 22 the C shock preceded the F shock. Time in 0.2 and 1. msec. below.

and of other experiments, in which it was found that the C shock may create a long-lasting facilitation of the F shock. For example, Fig. 8 reproduces records from an experiment in which the C shock was followed by a markedly enduring facilitation of the F response (1, 3, 4, 6), greater than the facilitation of the C response by the F shock (9, 10).

The striking difference between the experiments in Fig. 7 (13 to 20) and Fig. 8 (1, 3, 4, 6) finds its explanation in the fact that in Fig. 8 the C response



was followed by a period of increased tonic activity, obviously due to internuncial bombardment, while in Fig. 7 the C response was followed by a silent period which indicated absence of internuncial bombardment; even the trans-

mission of the tonic labyrinthine impulses had been blocked. Evidently the *c* volley in this experiment was not followed by internuncial volleys; while it arrived as well at motoneurons as at internuncials, the latter failed to respond, or if they did respond their impulses were blocked at some internuncial link made refractory by the shock (cf. 1936). Since the *f* volley, no matter how powerful it may be, in the absence of a background of subliminal stimulation cannot set up response in any motoneuron, the F response became "inhibited" as soon as the period of summation of the *c* and *f* volleys was finished. Comparison of records 20 and 21 demonstrates that summation was poor, indeed scarcely possible when the *c* and *f* volleys were delivered 0.2 msec. apart. This result and the "inhibition" of the F response in records 13 to 17 do not demonstrate that the *c* impulses did not cause a long-lasting lowering of threshold of some motoneurons, but they do demonstrate that if a long-lasting effect such as this had been produced, it was considerably weaker than the immediate effect of a mild (i.e., subliminal for the majority of the motoneurons), internuncial bombardment.

The limited strength of durable effects also is apparent after long-lasting bombardment of the motoneurons, as in the case of vestibular nystagmus. During that reflex the agonistic eye muscles show a series of slow contractions of long duration, interrupted by rapid relaxations of short duration—no more than 100 msec. Thus, it may be said that the motoneurons are submitted to a constant bombardment by impulses interrupted by short periods of no bombardment. Should continued bombardment after

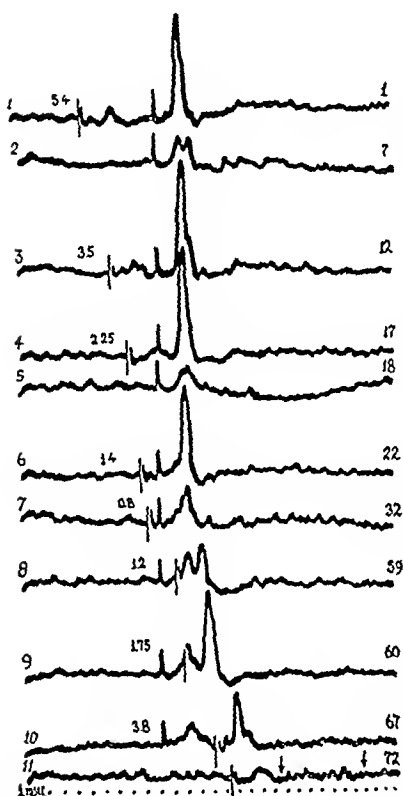


FIG. 8. Oculomotor preparation; responses recorded from the trochlear nerve (3-3-36). Two stimulating electrodes in positions F2 and Col. (Fig. 2) respectively. The F shock was maintained at the center of the oscillograph while the C shock was made to appear before (1 to 8) and after (9 and 10) the F shock at the intervals indicated in msec. on the records. 2, response to the F shock in isolation; 11, response to the C shock in isolation; note the increased tonic activity (between vertical arrows) following the *c* response. Time in msec. below.

it stops be followed by a long-lasting lowering of threshold, then during the periods of relaxation at least those motoneurons which did not fire during the

nystagmic contraction would respond to F shocks. But in fact they do not so respond; the response to an F shock is always large during the periods of contraction, while it is small or absent during periods of relaxation (1935a, Fig. 2).

Under the conditions of the present experiments, in which the stimulating shock always creates a powerful volley of impulses delivered to the motoneurons, facilitation and increase of the tonic waves in the electrogram of the motor nerve or the muscle have been inseparable phenomena, even when facilitation lasted for several seconds. For that reason, facilitation in every case could be explained as the result of instantaneous summation of the testing volley of impulses with impulses of the internuncial bombardment, the existence of which was revealed by tonic discharge of some motoneurons. Fig. 9 reproduces records from a representative experiment in which long-lasting facilitation was observed after a short tetanic stimulation through the C electrodes. In order to avoid strong motor reactions the preparation was kept under light ether narcosis, which is known to reduce the tonic internuncial activity.\*

Although during ether narcosis single F shocks are ineffective (Fig. 9, 11, 16) two F shocks in succession may set up strong responses (Fig. 9, 1), undoubtedly because the first shock starts an internuncial bombardment of the motor nucleus. Its duration is usually brief (from 1.25 to 5 msec.), the impulses being able to cross only a few internuncial synapses, but tetanic stimulation leads to the creation of internuncial bombardment and facilitation of several seconds' duration (Fig. 9).

As already mentioned, in the experiment illustrated by the records in Fig. 9 the conditioning tetanus was delivered through C electrodes, the C cathode being placed in front of the oculomotor nucleus, but far enough away to prevent electrical stimulation of motoneurons or motor axons. The response was recorded from the right internal rectus muscle. A series of C shocks at low frequency (Fig. 9, 2, 3) did not cause motor response or long-lasting facilitation of F shocks, but series of low frequency during the period of increased internuncial activity following a previous stimulus, or series at high frequency caused motor responses similar to those in Fig. 6 and also long-lasting facilitation of the F shock (Fig. 9, 5, 8, 13). During the period of facilitation, except in the silent period immediately following motor discharge, the electrogram of the muscle showed tonic waves caused by the response of a few motoneurons. Facilitation was strong while the tonic discharge was great (6, 9, 14), but it decreased when the tonic waves diminished in size (7, 10, 15), and disappeared when the tonic waves ceased (11, 16). It is important to mention

\* The effect of ether is rapidly apparent; it has, in fact, the effect of inhalation of a mixture of ether and air so weak that the corneal reflex after prolonged inhalation. A specific of the vestibular system must, therefore, be assumed. However, the motoneurons are but little affected, because they readily respond when internuncial bombardment is created by suitable stimulation. Furthermore, results similar to ether narcosis are obtained when the background of subliminal stimulation is suppressed by destroying the reticular substance in the pons. The selective effect of anesthetics is also suggested by the experiments of Bremer and Moldaver (1933).

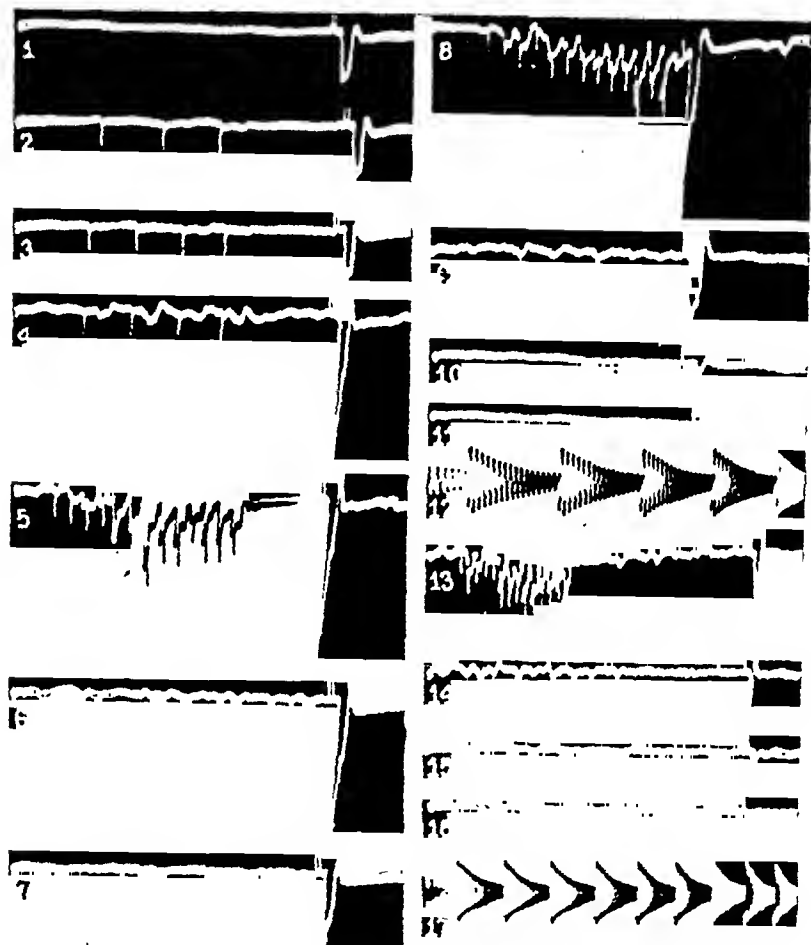


FIG. 9. Oculomotor preparation; responses recorded from the internal rectus muscle (negativity downwards). Two stimulating electrodes in positions F2 and Col. (Fig. 2) respectively (6-5-36). Light ether narcosis. 1, response to two F shocks in quick succession; 2, 3, the same response conditioned by a series of shocks through the C electrodes at low frequency; 4, the same as 3 but the series delivered during a period of internuncial activity following a previous C stimulation at high frequency. The F response is facilitated. 5, facilitation by a series of 13 C shocks at a frequency of 500 per second; 6, two seconds later; 7, four seconds later. Note the tonic activity in records 6 and 7. 8, 9, 10, 11, facilitation of the response to one F shock immediately and 2, 4 and 6 seconds after a series of 13 C shocks at a frequency of 475 per second. Note that the F shock remained ineffective (11) when the electrogram of the muscle did not reveal the existence of tonic discharge. 12, timing film (1/60 and 1/1000 second) for records 1 to 11; 13, 14, 15, 16, a similar set of records, also obtained at two second intervals, illustrating facilitation of a subliminal F shock (16) after delivery of tetanic stimulation (13) through the C electrodes; 17, timing film (1/60 second) for records 13 to 16.

that each facilitated response (6, 9, 13) was followed by a silent period in the electrogram, indicating that the impulses set up by the F shocks fired those motoneurons which were taking part in the tonic discharge. Here again facilitation extended only to the motoneurons reached by large internuncial volleys.

In view of the evidence presented here the conclusion must be reached that the internuncial bombardment, despite the short duration of the effect

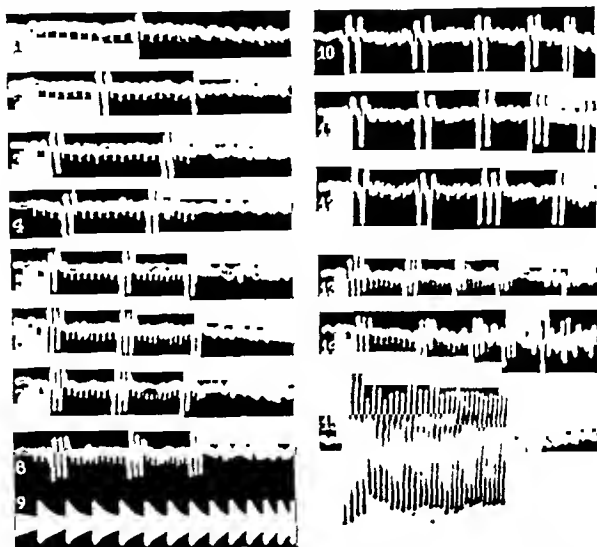


FIG. 10. Oculomotor preparation; responses recorded from the internal rectus muscle (negativity downwards) (6-1-36). Tetanic stimulation through the C electrodes. Time (1/60 second) in record 9. The small sharp downward deflections are shock artifacts. Further explanation in text.

of the individual impulses, constitutes a statistically constant stimulus for the motoneurons of the active group; each neuron responds to it rhythmically at a frequency determined by two factors: (1) strength of the bombardment and (2) rate of recovery of the neuron. An almost ideal confirmation of this conclusion is given by the records in Fig. 10. The cathode of the stimulating (C) electrodes was placed near the oculomotor nucleus, so that certain motoneurons were capable of responding to the summated effect of induction shocks and internuncial impulses.

In records 10, 11, and 12 the shocks were strong enough to stimulate some motoneurons. The responses did not, however, follow the rhythm of the stimulating series; they appeared in groups of two and sometimes three responses, separated by intervals including four or five shocks during which only a mild tonic discharge was visible. The grouping of discharges was obviously attributable to summation of subnormality; two or three responses in quick succession raised the threshold of the motoneurons to a high level and no further response could take place until the threshold had recovered.

In records 1 to 8 the strength of the shocks was reduced so that they did not reach the electrical threshold of the motoneurons without first increasing the internuncial bombardment. The frequency of the stimulating series was progressively increased from record 1 to record 8. In record 1 the electrical threshold of the motoneurons was not reached until the tenth shock of the series, and it was not attained again during the remainder of the series. In record 2 the response appeared earlier (seventh shock) and there was a grouped discharge followed by a long silent period. A similar effect is seen in records 3 and 4. In record 5 the frequency of the series was sufficient to create a strong internuncial bombardment, with the result that the responses were regularly grouped in pairs. Nevertheless two responses in quick succession were sufficient to create a subnormal threshold which remained for periods of over 40 msec. above the stimulating value of the shocks.

Further increase in the frequency of the series (6, 7, 8) reenforced the internuncial bombardment to a degree so that the groups of responses contained three equal twitches, but here again after the third twitch the threshold of the motoneurons became so high that a silent period, of 40-50 msec. duration, followed each third twitch. While records 1 to 12 were being taken, the preparation was kept under mild ether narcosis which prevented the increase of internuncial activity above unwanted limits; but before taking records 13 to 15, the narcosis was discontinued. The strength of the shocks was reduced below the value used for records 1 to 8; nevertheless the groups of responses contained three or four twitches before subnormality increased sufficiently to prevent further response. The great amount of internuncial activity created by the series of shocks also revealed itself in the powerful tonic discharge lasting throughout the series.

Although the records were obtained at two-second intervals, the effect of the stimulus was cumulative and the tonic discharge at the end of the series increased progressively in each record (13, 14). Finally, in record 15 the internuncial bombardment was so great that the three first shocks of the series reached the threshold of all the motoneurons of the nucleus, resulting in an abortive group formation; but the internuncial bombardment raised the stimulating effect of the shocks to maximal value and the remainder of the response consisted of maximal twitches at the frequency of the series. The internuncial activity was so great that despite the high threshold of the motoneurons no silent period appeared after withdrawal of the stimulus. Furthermore it continued to increase and soon spread through the whole

reticular formation, with the result that the preparation showed violent convulsions.

The grouping of discharges also may be observed in the pure synaptic responses of motoneurons. In the experiment shown in Fig. 11 the responses were recorded from the right trochlear nerve; the C cathode was placed in front of the right oculomotor nucleus. In record 1 the frequency of the series (about 300 per second) was almost subliminal, only two small responses being present after the sixth and the tenth shock. Strong responses began to appear

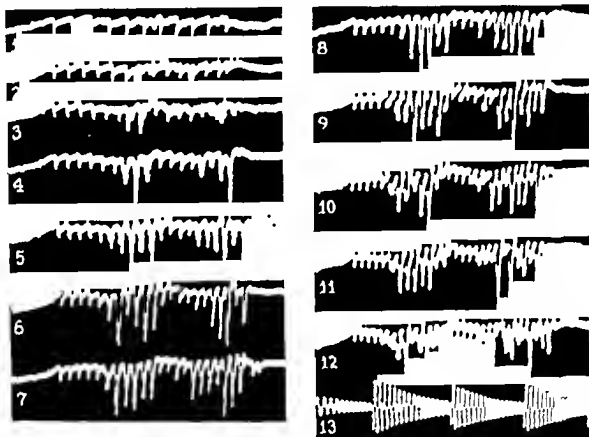


FIG. 11. Oculomotor preparation; responses recorded from the trochlear nerve (negativity downwards (2-13-36)). Tetanic stimulation through the C electrodes. Time (1/60 and 1/1000 second) in record 13. The small sharp downward deflections are shock artifacts. Further explanation in text.

in record 3 when the frequency of the series was about 350 per second; the discharge of the motoneurons took place in two groups separated by an interval of about 15 msec. Increase in the frequency (4, 5, 6) caused the responses to appear early and to grow in size, but it did not change the grouping of the discharge. At high frequencies the discharges, although clearly grouped as before, became irregular (11, 12).

The mechanism of the production of groups is understandable. Single shocks being ineffective to create sufficient impulses to reach the threshold of the motoneurons, successive recruitment was necessary, until finally the internuncial bombardment became strong enough to bring the threshold of the motoneurons down to the stimulating value of the volleys created by the C shocks. But the tetanic activity of the internuncial neurons soon created in them a high threshold, with the result that the internuncial impulses were

blocked at some of the cells and the bombardment ceased. Response of the motoneurons could not take place until after a second period of recruitment. This effect is very interesting in that it reveals the existence of a process by means of which a pool of internuncial neurons may reduce the frequency of the impulses it transmits at the same time that it changes the character of the afferent stream from a practically continuous bombardment by asynchronous impulses into a series of powerful volleys of synchronous impulses at low frequency.

#### DISCUSSION

(a) *Bombardment of motoneurons by internuncial impulses as a source of continuous stimulation.* The period of summation of the impulses arriving at neighboring synapses is short. For example, in the experiment illustrated in Fig. 7, 20 and 21, most of the *f* and *c* impulses failed to summate and to reach threshold when delivered at 0.2 msec. intervals. Nevertheless internuncial bombardment may constitute a constant stimulus, because the great number of internuncial cells ensures the delivery of impulses in large numbers and at high frequencies. For example, in the case of Fig. 3, following the initial *f* volley, internuncial impulses entered the motor nucleus in successive volleys at intervals of about 0.7 msec., which is the average delay of internuncial neurons. Furthermore, the internuncial volleys, owing to slight differences in the delays at the individual neurons and to differences in the speed of conduction in axonal branches of various calibers, necessarily were highly asynchronous. The frequency of arrival of the impulses at the individual neurons was correspondingly high, for the frequency of the wavelets in records 5 and 6 in Fig. 3 was over 2000 per second, and the majority of the internuncial impulses remained below threshold for the motoneurons. Thus it may be said that the internuncial impulses arrive at the individual motoneurons in a constant stream, so that the *f* impulses created by the second, testing, *F* shock, delivered at any moment during the period of facilitation which follows the conditioning shock, always meet at the motoneurons internuncial impulses with which they can sum. The situation is exactly the same for the internuncial neurons, because as previously mentioned (Fig. 2), all the fibers having synapses on motoneurons also have synapses on internuncial cells, so that whenever motoneurons receive impulses at their synapses, internuncial neurons necessarily are also stimulated.

The shortness of the period of effective summation of two impulses excludes the possibility of the summation of impulses that have arrived in succession through the same fiber. Hence the strength of the stimulation by internuncial bombardment depends upon the density of the latter, *i.e.*, on the number of fibers conducting impulses simultaneously; and all gradations are possible, ranging from subliminal (*i.e.*, only maintaining facilitation) to liminal (*i.e.*, causing discharge of resting neurons) and supraliminal (*i.e.*, causing discharge of refractory neurons). Internuncial bombardment must necessarily cause rhythmic discharge of motoneurons, because each responding motoneuron will fire again as soon as its threshold is reached by the stimulus.

Internuncial bombardment (Forbes, 1922; but cf. Forbes, 1934, 1936) has all the properties of *c.e.s.* (Sherrington, 1925; Eccles and Sherrington, 1931b; Bremer and Homès, 1932), and since a motoneuron despite any possible lowering of threshold due to previous, intrinsic or extrinsic activity does not fire unless impulses are delivered to its synapses (cf. 1938b), there is no doubt that the "central excitatory state" leading to motor discharge is due to internuncial activity and bombardment. Furthermore, it has been shown in this paper that subliminal *c.e.s.*, *i.e.*, excitation demonstrable only by its ability to facilitate the response to an intercurrent stimulus, is always accompanied by internuncial bombardment, which under the conditions of the present experiments overshadows the effect of any other factor capable of lowering the threshold of the neurons.

For this reason the present discussion is conducted on the following principles: *The mechanism of the stimulation of neurons is the delivery of impulses at their synapses. The effect of the individual impulses is brief, but the continuous arrival of impulses ensures constant stimulation. The neuron responds whenever the stimulating effect of the impulses that arrive within a period of effective summation reaches its threshold.* The neurons as well as their axons (Gasser, 1935a, b; cf. Eccles, 1936b, p. 392) have two thresholds, the resting and the subnormal threshold which develop during tetanic activity (Lorente de Nó and Graham, 1938). The creation of a high subnormal threshold does not necessarily demand a long-lasting activity; two discharges at high frequency are sufficient to raise the threshold of the motoneurons to a high level (*loc. cit.*, Figs. 5 and 6).

The existence of a third threshold, even lower than the resting threshold, although it has not yet been demonstrated for motoneurons is likely, because it has been found to exist with sympathetic ganglion cells, with the neuromuscular junction, and with nerve fibers. With sympathetic ganglion cells Eccles (1936a, b, 1937b) observed after delivery of subliminal synaptic stimuli at the end of the period of effective summation, which Eccles has called summation of detonator responses, a second period of summation termed by him *c.e.s.*,\* that appeared to be caused by a lowering of threshold of the ganglion cells. It never resulted in the setting up of an impulse. Bremer and Kleynjens (1937) offer convincing arguments in favor of the view that the process underlying this second period of summation is the same as the process responsible for the passage of a second impulse across the partly curarized neuromuscular junction of the frog (Bremer, 1930; Bremer and Homès, 1932), or the neuromuscular junction of the crab (Lucas, 1917).

With nerve (Gasser, 1938), a second period of summation after subliminal stimulation can regularly be demonstrated under certain conditions, for example, after tetanization. Therefore the assumption lies at hand that the second period of summation is a general property of excitable tissues which

\* The suggestion of Eccles to apply the term *c.e.s.* to the second period of summation is not followed here, for the reason that the term has been widely used with a different significance.



may influence synaptic transmission. However, in blood-perfused trochlear nerve the second period of summation is not demonstrable unless the recovery curve shows a supernormal phase, or unless the nerve has previously been tetanized (1938e). Under ordinary conditions it is absent; absence of peripheral recruitment is shown in Fig. 6. On the other hand, the effect of the lowering of threshold during the second period of summation is qualitatively the same as a mild internuncial bombardment (cf. Bremer and Kleyntjens, 1937, Gasser, 1938), and consequently not demonstrable in the presence of the latter (cf. Eccles, 1936b, p. 376). Since under the conditions of the experiments reported here the internuncial bombardment is always present, there is no immediate need for considering the second period of lowered threshold; although it is realized that under given conditions it might play a pre-eminent role. For example, the remarkable observation of Kleyntjens (1937) made on the frog that tetanization of the motor nerve increases the reflex response, indicates that at least under certain conditions, after prolonged tetanization a period of lowered threshold develops in the motoneurons. Another factor likely to play an important role in determining the threshold of the neurons is a change of metabolic conditions (Dusser de Barenne, McCulloch, and Nims, 1937). Its significance is not minimized by disregarding it in the present discussion, but more precise information is needed before it can be successfully considered in theoretical arguments.

The main difference between the concept of *c.e.s.* as used by the Oxford school (Creed *et al.* 1932) and that of continuous stimulation by internuncial bombardment is that *c.e.s.* was assumed to develop and accumulate within the individual neurons, while internuncial bombardment places the excitatory and facilitatory mechanisms outside of the cell (1935b, p. 607). For many theoretical arguments the difference may be overlooked; in fact, the result obtained is essentially the same, whether the one or the other concept is used. In his review Eccles (1936b), while re-examining the physiology of the spinal cord in the light of recently acquired knowledge, found it necessary to alter but few of the original theoretical arguments. The concepts of recruitment, fractionation, subliminal fringe, etc. can be kept with their original meaning and have been repeatedly used in this paper. Nor is it necessary to alter the discussion of the transmission of impulses across the cerebral cortex made elsewhere (1934a) on the basis of Sherrington's *c.e.s.* As a matter of fact, if the recruitment and successive fractionated discharge of the various groups of cortical neurons had to be described entirely in terms of the internuncial bombardment responsible for it, the diagrams, owing to the very large number of neurons to be considered, would lose their didactic value.

However, there are cases in which the concept of *c.e.s.* as an enduring state of excitation of single cells cannot be used, not even to simplify theoretical arguments, as for example, when the simultaneity of arrival of two volleys of impulses is the necessary condition for threshold stimulation (cf. later discussion of inhibition), or when the response of the neuron depends more on

the spatial distribution of the active synapses than on the total number of impulses (1938c).

(b) *The multiple chains of internuncial cells* (M, Fig. 2) as *elementary units of transmission*. The question so often mentioned in the literature, as to whether a two-neuron (one synapse) arc sets up motor responses, can now be satisfactorily answered. Since the temporal summation of impulses arriving in succession through the same synapse is hardly possible, there can be no doubt that some cells in the nervous system are stimulated above threshold when a sufficiently strong synchronous volley of impulses through a homogeneous path is delivered to them. Obviously the cells with one-to-one transmission are those having either large synapses with individual fibers, or those having large sections of their soma covered by synapses of fibers from one homogeneous pathway (1933b). The rest of the neurons will fire only when impulses arrive simultaneously through several different pathways.

In the spinal cord it can be established (1938c) that the motoneurons have synapses of heterogeneous origin, so that conduction of impulses through a single pathway cannot result in the activation of all the synapses in any discrete zone of the soma, while many internuncials, especially in Cajal's intermediate nucleus and in the posterior horn, have homogeneous synapses. These cells must fire when a sufficiently large synchronous volley of impulses enters into the cord through the posterior roots; and in fact they do so, because (1) subliminal stimuli cause facilitation, and (2) internuncial potentials precede motor discharge and are obtained at a lower strength of stimulation (Gasser and Graham, 1933; Hughes and Gasser, 1934a, b).

When anatomical conditions prevent the convergence of impulses and therefore make it impossible for a two-neuron arc, such as that formed by fiber  $f$  and the motoneuron of Fig. 3, to transmit impulses, the additional activity of one internuncial neuron ( $i_1$ , Fig. 3) may result in transmission. If the first impulse through fiber  $f$  fires cells  $i_1$ , the motoneurons will respond to a second  $f$  impulse arriving simultaneously with the  $i_1$  impulses, but obviously a transmission unit containing only one internuncial neuron cannot transmit impulses at a frequency below 1000 impulses per second. Increase in the number of links in the internuncial chains diminishes the frequency, and yet in the case of the oculomotor preparation, the frequency of shocks delivered to the posterior longitudinal bundle and adjacent pathways must be rather high, i.e., 100 per sec. (Figs. 6 and 9.) Transmission of impulses at lower frequency demands the activation of much more complex chains of neurons, which are found only in the so-called primary nuclei of the sensory nerves—the posterior horn of the spinal cord, etc. The urgent need for including in physiological diagrams these nuclei, which form the most complex part of the medulla and cord, is herewith emphasized.

The concepts of the two-neuron arc, or of an arc with a fixed number of internuncials, lose their physiological meaning. On the one hand the impulses may set up responses of the motoneurons after having crossed a variable num-

ber of synapses, depending upon the state of the centers; and on the other hand, the internuncials are not intercalated between afferent fibers and effector cells. They form collateral chains superimposed upon the shortest path which, if a sufficient background of facilitation exists, is undoubtedly passable.

(c) *Fractionation of the internuncial and motor pools into active and inactive groups.* The elementary phenomenon responsible for fractionation consists in this, that threshold stimulation of a neuron is obtained only by summation of impulses delivered at several synapses. Of the neurons reached by the fibers of the active tracts only those respond upon which convergence of impulses takes place; the other neurons remain in the subliminal fringe (Sherrington, 1931). However, since each internuncial axon branches out and establishes connections with a large number of other internuncial neurons, it is difficult to understand how during continued stimulation the impulses may fail to spread into neighboring channels and engage a progressively increasing number of neurons producing avalanche conduction (Cajal, 1909; Herrick, 1926).

The fractionation of the neurons of a pool into active and inactive groups is found not only in reflex physiology, but is a general feature of the activity of the nervous system. A most demonstrative example is the recent observation of Marshall, Woolsey and Bard (1937; cf. Bard, 1938) on the physiological projection of the surface of the body onto the sensory cortical areas. Despite the many possible channels for the dispersion of impulses, only a discrete portion of the cortex becomes active. This indicates that here, as in the case of the retinal projection, the fractionation is successively maintained in each internuncial station (cf. 1934b, Fig. 36).

One of the most remarkable features of fractionation is that, once established, it continues in the absence of peripheral stimulation. For example, stimulation of a single semicircular canal results in a response of the motor apparatus of the eye producing nystagmus with a component, the "nucleus," invariable for each canal and another component, the "appendage," which may be reversed by concurrent stimulation of another canal (1933e) or even by stimulation of static receptors (1931). The interesting fact is that if the appendage of a response has been reversed by the concurrent stimulation of another canal, the reversal is maintained after concurrent stimulation stops. Likewise, the appendage of a response may be reversed by the after-discharge of a previous stimulation. This indicates that certain labyrinthine impulses may enter into two different channels, but once they have entered one of them they do not leave it during the remainder of the response. Even more, they force other impulses to use the same channel, with the result that they summate; and two stimuli in isolation apparently antagonistic, when delivered simultaneously give rise to a stronger response.

How the reversal is initiated it is not difficult to understand. In Fig. 12,  $f_1$ ,  $f_2$ , and  $f_3$  are fibers of the vestibular nerve and it is assumed that two synapses must be activated in order to insure the passage of the impulse across the synapse. It is clear that stimulation of fiber  $f_2$  will always fire cell  $N$ , setting up the nucleus of the response and that concurrent stimulation of

fibers  $f_1$  and  $f_2$  will cause response of cell 1, setting up the appendage  $A_1$ , while concurrent stimulation of  $f_2$  and  $f_3$  must set up appendage  $A_2$ .

Now it is known (1933c, Figs. 4 and 8) that the pools of neurons of the reticular formation send numerous recurrent (centrifugal) fibers back to the primary nuclei, thus forming a closed chain of type *C* (Figs. 2 and 12); and

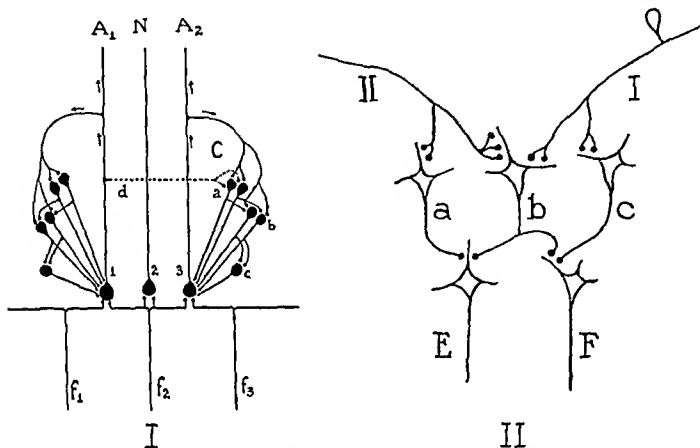


FIG. 12. I. Diagram explaining the production of reflex reversal by concurrent stimulation of two fibers ( $f_1$  and  $f_2$  or  $f_2$  and  $f_3$ ) from different peripheral sense organs and its maintenance by the impulses conducted by closed chain *C*, after fiber  $f_3$ , which initiated the response of cell 3, ceases conducting. Each one of the links in the closed chain represents a multiple chain of neurons (*M*, Fig. 2) such as is illustrated in the diagram of Fig. 3. Collateral *d* by lowering the threshold of cell *a* and thus causing two impulses to cross through cell 3 in quick succession may produce inhibition, for cell 3 will acquire a high subnormal threshold.

II. Diagram of Gasser (1937c) explaining reciprocal innervation. It is assumed that threshold stimulation of neurons with normal threshold requires simultaneous activation of two synaptic knobs, but three knobs are required to stimulate a neuron having subnormal threshold. When fiber I conducts a rhythmic series of impulses at low frequency neuron *F* is stimulated by the *b* and *c* impulses and the flexor muscle contracts, but if fiber II then becomes active, cell *b* will be forced to discharge an extra impulse and to acquire subnormal threshold. Henceforth cell *b* will be able to respond only to the impulses conducted by fiber II, the result being that the extensor muscle contracts, while the flexor muscle relaxes because the *b* and *c* impulses reach neuron *F* at intervals longer than the period of effective summation of impulses delivered at neighboring synapses.

it is also known (1928, 1931, 1933) that lesions in the reticular substance, destroying among others those recurrent pathways, modify the transmission of impulses through the primary nuclei. The assumption lies therefore at hand that when the  $f_3$  fiber stops conducting, the impulses brought back to the vestibular nuclei through the *C* chain maintain the state of facilitation of cell

3 and raise to threshold value the stimulating effect of the  $f_2$  impulses, which continue setting up the appendage  $A_2$  as if the  $f_2$  impulses were still being delivered.

In systems having an extensive anatomical distribution such as the internuncial nuclei in the medulla and pons or in the spinal cord, analysis of the individual closed chains of neurons cannot be made, but in other organs, such as the cerebral cortex, the study may be carried out much farther. It is found (1934a, 1938d) that the arrangement of afferent fibers and cortical dendrites and axons in closed chains is such that the successive volleys of internuncial impulses must be delivered again and again in great density to the cells—internuncials and effectors—reached by the afferent volley, while the neighboring cells, which receive only small and infrequent volleys, must remain in the subliminal fringe. Thus it must be concluded that in the cerebral cortex the arrangement of the internuncial cells in closed chains, which force the impulses to use the same pathways repeatedly, is an anatomical mechanism leading to fractionation; and there is evidence to show that the same mechanism is operative also in subcortical centers.

(d) *Long-lasting facilitation, after-discharge.* At present it is generally believed (cf. 1935c; Eccles, 1936b, p. 394; Fulton, 1938 Chap. IV) that long-lasting facilitation and after-discharge are maintained by internuncial bombardment. The bombardments of relatively short duration can be satisfactorily explained by open chains of neurons having a few links. As a rule (cf. Kemp, Coppée and Robinson, 1937) it may be calculated that the passage of impulses through each internuncial station in the medulla and midbrain demands 1 msec. or slightly more (synaptic delay plus conduction time). Consequently, open internuncial chains such as are illustrated in Fig. 3 will be able to maintain facilitation and after-discharge for 4 msec. But long-lasting bombardment necessarily demands repeated passage of the impulses through the same internuncial cell (Bremer and Rijlant, 1926; Forbes, Davis, and Lambert, 1930). The internuncial chains through which the impulses circulate have been called reverberating circuits (Ranson and Hinsey, 1930) and closed self-reexciting chains (1933c).

Since the summation of subnormality progresses but slowly at low frequencies, a closed chain having a large number of links can remain in activity for considerable periods of time; but short chains, in which the impulses circulate at high frequency, must have a short time constant, because the passage of only a few impulses will create a high threshold and stop conduction. Inhibition must then result (1936). For example, in the diagram of Fig. 12 impulses may circulate through the closed chain  $C$  at different rates. If the circuit should be closed through cells  $a$  the rate would be high, because the impulse initiated in cell 3 would return in about one msec. to the same cell after crossing cells  $a$ ; but if the cell 3 impulse should fail to reach the threshold of cells  $a$  and return through  $b$ , the rate would be lower. With a long chain, i.e., one with many internuncials in series, or a chain including long fiber paths, the rate of circulation may be low enough to allow activity for considerable

periods of time, especially when fiber  $f_2$  or  $f_3$  also is conducting a series of impulses. However, if while chain  $C$  is working at low frequency, facilitation of cells  $a$  by impulses through collateral  $d$  should force the impulse from 3 to cross these cells and to restimulate cell 3, the activity must cease, because two discharges at the rate of 1000 per second create in cell 3 so high a threshold that further transmission through this cell is blocked.

Thus, the activity of closed chains of internuncial neurons leads, under certain conditions, to facilitation, and under other conditions to inhibition. For this reason it seems best to drop the qualifications "reverberating" and "self-reexciting," which have too strict a meaning. The function of the closed chains of neurons must be analyzed in each particular case, as it must be determined by experiment whether a certain system of closed chains may become rhythmically active in the absence of peripheral stimulation or of impulses arriving from other centers.

There is evidence that in the case of the internuncial system regulating the discharge of ocular motoneurons, the closed chains of neurons in the reticular formation and vestibular nuclei are dependent for the initiation and maintenance of their activity on the constant stream of impulses set up in static receptors such as the labyrinth, the proprioceptors of the neck muscles, etc., so that even when by suitable operation the closed chains are made short, their activity may continue for long periods of time. This point deserves detailed consideration, for it leads to the problem of the nature of after-discharge. Is after-discharge the continuation of a newly created activity, or is it simply a particular case of reflex reversal which maintains the impulses, ordinarily passing through certain channels, in another set of channels?

It has been shown (1928, 1933c, p. 22) that vestibular after-discharge may be enormously prolonged by destroying parts of the reticular formation. The neurons left after the operation still formed closed loops (1933c, Fig. 8) but evidently short ones. With the now available knowledge of the recovery cycle of motoneurons, if an attempt is made to explain the after-discharge in terms of autochthonous activity of the closed circuits, the result becomes paradoxical. The destruction of internuncial cells shortens the chains and favors the creation of a high, subnormal threshold, because in order to maintain the internuncial bombardment, the remaining neurons must discharge at high frequency; nevertheless, the after-discharge is prolonged. The explanation is prompted by diagram I of Fig. 12, which indicates that if impulses started somewhere else are fed into them, the closed chains do not need to maintain circulation of impulses at the high frequency which autochthonous activity would demand. Fiber  $f_2$  now represents one of the fibers from static labyrinthine receptors which set up the tonus of the external rectus eye muscle by firing the few motoneurons reached by the axon of cell  $N$ . The intercurrent stimulation of fiber  $f_3$  brought in the motoneurons innervated by  $A_2$ , and the contraction of the muscle increased. When the stimulus of fiber  $f_3$  was withdrawn, the impulses conducted back to the primary nuclei through the  $C$  chain maintained facilitation of cell 3 and the  $f_2$  impulses were still capable

of crossing that synapse, with the result that muscle remained contracted (after-discharge) until subnormality was created in some neuron of the *C* chain. If the bombardment of cell 3 by the *C* chain (cells *a*, *b* and *c*) is mild, the  $f_2$  impulses will set up discharges of cell 3 at low frequency; but under ordinary conditions, when the *C* chains are complete, many synapses of the  $\beta$  cells are simultaneously activated and the impulses are forced to circulate at higher frequency. The result is that subnormality is more rapidly created and after-discharge stops earlier.

In how far this argument applies to the spinal cord cannot be determined without direct experiments. It is likely, however, that the argument has general application, for the reason that long-lasting after-discharge hardly ever appears without a background of tonic activity (decerebrate rigidity, etc.), which obviously is due to a continuous stream of impulses arriving either from the periphery or from other centers.

(e) *Rhythmic reflexes*. Stimulation of the semicircular canals results in a rhythmic reflex, nystagmus, characterized by a succession of contractions and relaxations of the eye muscles. The records of the action potentials of the eye muscles or of their motor nerves during nystagmus are similar to the records in Figs. 10 and 11, the similarity being enhanced by the fact that the grouped discharges in Figs. 10 and 11 were obtained during continuous stimulation in the same way as nystagmus is produced in the presence of a continuous stream of labyrinthine impulses. Both sets of phenomena seem to have the same explanation.

In the classical theory of the production of rhythmic reflexes (Graham Brown, 1914; Forbes, 1922; Spiegel, 1929) the attempt was made to explain simultaneously reciprocal innervation and rhythm on the basis of a succession of states of activity and rest, as due to the fatigue of certain cells. This explanation is consistent with present knowledge, although rhythm and reciprocal innervation must be accounted for separately. Rhythm is generally accompanied by reciprocal innervation but it may appear without it, even when the antagonistic muscles contract and relax simultaneously. The following discussion, therefore, refers to a frequent form of nystagmus which is perhaps the fundamental one, in which the agonist muscle shows a succession of slow contractions and quick relaxations of short duration, while the antagonist muscle shows only quick contractions (Fig. 13, II; cf. 1935f).

A number of significant facts are known: (1) During the slow phase of nystagmus the contraction of the agonist is due to an increase of the number of active motor units and to an increase in the frequency of their discharge. The speed of the contraction, *i.e.*, the speed of the recruitment of the motor units, is directly proportional to the strength of the stimulus, while the duration of the contraction is inversely proportional to it. Many things seem to indicate that the onset of the quick phase is caused by a trigger-like mechanism, which becomes active when the contraction has reached a certain level dependent upon the strength of the stimulus. (2) The relaxation of the agonist and the contraction of the antagonist during the quick phase are very fast,

*i.e.*, the recruitment of the motor units of the antagonist proceeds rapidly, the discharge of the motoneurons taking place with a great deal of synchronism. The duration of the quick component varies between narrow limits (McCouch and Adler, 1931) from 100 msec in weak nystagmus to 80 msec in strong

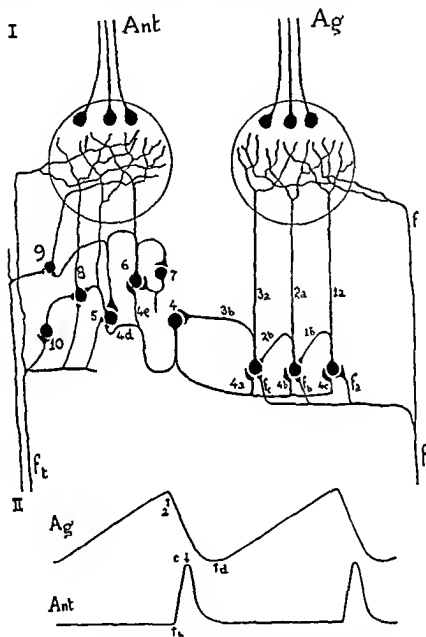


FIG. 13 I Diagram explaining the production of rhythm during vestibular nystagmus. Fiber *f* is supposed to carry the continuous series of impulses started at the cristae of the semicircular canals which set up the nystagmus. Fibers *f<sub>i</sub>* are supposed to be maintaining the tonus of the antagonistic muscle, 1*a*, 1*b*, 2*a*, 2*b*, 3*a*, 3*b* are branches of the axons of cells 1, 2 and 3. 4*a*, 4*b*, 4*d*, 4*e* are branches of the axon of cell 4. *f<sub>a</sub>*, *f<sub>b</sub>*, *f<sub>c</sub>* are branches of fiber *f*.

II Diagram of the rhythmic succession of contractions and relaxations of the antagonistic muscles during the nystagmus explained by diagram I. Rising of the line indicates contraction. The interval between turning points *a* and *b* is never less than 3 to 4 msec, the interval between turning points *c* and *d* may be 50 msec long.



nystagmus (1935f). (3) The stream of impulses created in the vestibular nuclei is a constant one. The interrupted discharge of the motoneurons is attributable to the activity of neurons located in the reticular formation. In fact, if part of the reticular formation or of its pathways is destroyed, the nystagmus is converted into a monophasic reflex, the agonist remaining contracted as long as the peripheral stimulus lasts (1933c). (4) The relaxation of the agonist is not attributable to an active inhibitory process but only to a lack of excitatory impulses (1933d). (5) The turning points in the antagonistic muscles are not synchronous (1935f) (Fig. 13, II).

In view of these facts it is not difficult to construct a diagram explaining the production of rhythm. In Fig. 13, *f* represents the fibers of the semicircular canals which, after interruption in the primary vestibular nuclei, reach the motor pool of the agonist and the internuncial pool (cells 1, 2, 3). In order to simplify the diagram, only a few internuncial cells have been included and it must be assumed, therefore, that, although successive impulses through the same synapse never summate, the period of summation of impulses arriving through different synapses is of long duration. This is identical with making the linkage between neurons through chains of type *M*, as in Fig 3. Cells 4 and 5 to 9 also belong to the internuncial system, and fibers *f*, represent those from static receptors such as the labyrinth and proprioceptors of the neck, which maintain the tonus of the antagonist. The effectiveness of stimulation is indicated by the size of the synaptic knobs. It is assumed that the synapses formed by a large terminal knob, representing a number of simultaneously active ordinary knobs, are one-to-one synapses, while those formed by small knobs demand summation of the effects at two adjacent knobs in order to fire the underlying neuron.

When fiber *f* starts to conduct, its rhythmic series of impulses successively recruits internuncial and motoneurons: the first *f* impulse does not set up any response of motoneurons, neither does it fire cells 2 and 3, but it fires cell 1; the second *f* impulse summates with the impulses delivered by the branches of 1 and fires some motoneurons and cells 1 and 2; the third *f* impulse summates with the impulses of 1 and 2 and fires a larger number of motoneurons and cell 3. The fact that cell 3 responds means that after completion of its synaptic delay cell 4 also fires and consequently cells 1, 2, and 3 must fire again. For this reason the fourth *f* impulse finds the motor nucleus in a greater state of facilitation, as it has just received two impulses from each internuncial cell and is capable of setting up a response of a large number of motoneurons. The contraction of the muscle is then strong; but, a relaxation must immediately follow because the discharge of two impulses by cells 1, 2, and 3 in quick succession, at an interval of about 1.2 msec., which is equal to the synaptic delay at 4 plus the synaptic delay at 3, 2, or 1, has created in them a strong subnormality, so that the *f* impulses cannot reach their threshold. Consequently since no internuncial impulses are produced, the facilitation of the motor nucleus ceases and the following *f* impulses alone fail to set up a response of the motoneurons. As long as the subnormal state of neurons 1, 2,

and 3 lasts, i.e., no more than 100 msec., the muscle remains relaxed, but as soon as recovery has been completed the same process is started once more; internuncials and motoneurons are successively recruited\* and the contraction of the muscle increases until the discharge of 4 again creates a state of subnormality in 1, 2, and 3. Evidently if by means of suitable lesions the connections of cell 4 with cells 1, 2, and 3 are severed, a sudden development of subnormality becomes impossible and the muscle will remain contracted as long as the  $f$  impulses are being produced.

The contraction of the antagonist is explained by the existence of branches 4d and 4e of the axon of cell 4. When this cell fires it not only causes the relaxation of the agonist, but also produces a contraction of the antagonist, for it sets into activity chains of neurons 5-6-7 which on the one hand deliver volleys of impulses to the antagonistic pool and on the other hand lower the threshold of cells 8 and 9, thus increasing the transmission of the tonic ( $f_i$ ) impulses to the motor pool. The antagonistic muscle contracts rapidly, but it must relax again very soon because the impulses cross through the short chains formed by cells 5 to 9 at high frequency and the rapidly created subnormality prevents further conduction of impulses to the motoneurons.

There is extensive experimental evidence to show that neurons 4 to 8 are located at least in part in the reticular substance in the pons. Moreover, it was found possible to place lesions in the vestibular system allowing those groups of neurons to become rhythmically active in the absence of stimulation of the semicircular canals (1928, p. 90; 1933c, p. 29). The eye muscles showed then a peculiar form of nystagmus; the antagonistic muscles underwent a rhythmic succession of fast and short-lasting simultaneous contractions, separated by longer phases of relaxation. Stimulation of the labyrinth did not produce any other result than increase of the frequency of the contractions; but when an additional part of the reticular substance was destroyed, the spontaneous nystagmus ceased and the labyrinth was again able to produce either a monophasic reflex consisting of a steady contraction of the agonist, or even a rhythmic nystagmus in which the contraction of the agonist was partially checked by small quick relaxations.

The relaxation of the agonist begins earlier than the contraction of the antagonist, because the discharge of cell 4, which makes cells 1, 2, and 3 subnormal, does not result in contraction of the antagonist until after some recruitment has taken place in chains 5 to 7. The interval between the beginning of relaxation of the agonist and the start of contraction of the antagonist is smaller the stronger the nystagmus, but even in the case of a strong reflex the difference is not less than 3 to 4 msec., indicating that the transmission of impulses from cell 4 to the antagonist pool takes place through at least three or four internuncial neurons.

After its relaxation the agonist again begins to contract when cells 1, 2,

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\* It should be noted that the period of relaxation of the agonist is made up of two parts: (1) the time during which the transmission of impulses is blocked; and (2) the time necessary for the recruitment of internuncial neurons.

and 3 recover from subnormality, while the contraction of the antagonist ceases when cells 5 to 7 become subnormal. Since the creation of subnormality demands less time than recovery from subnormality, it is to be expected that the contraction of the antagonist should be briefer than the relaxation of the agonist. In fact differences as great as 50 msec. have been found.

Despite its simplicity, the diagram in Fig. 13 explains why the rhythm may be profoundly modified by intercurrent stimuli. The rate of recruitment of neurons 1 to 4 and of neurons 5 to 9 depends not only upon the impulses conducted by fibers *f*, but also upon the impulses conducted by all the other fibers having connections with the internuncial cells; and the amount of subnormality necessary to block conduction of impulses also depends upon the amount of pre-existent internuncial activity.

Although the available information, especially the anatomical data, is not sufficient to warrant the application of the diagram given in Fig. 13 to other rhythmic activities of the nervous system, it seems likely that some of the elementary phenomena are in every case essentially the same (cf. Sherrington, 1906; Wachholder, 1924; Bronk and Ferguson, 1935) and that other rhythmic reflexes differ from nystagmus only in the rates of recruitment of the motor units during the alternating phases.

(f) *Inhibition, reciprocal innervation.* At present it is generally believed (cf. Eccles, 1936b; Beritoff, 1937; Fulton, 1938; Lorente de Nó, 1936) that specific inhibitory impulses, even if there were specific inhibitory fibers (Kato, 1934), do not exist. Inhibition must, therefore, be explained in terms of processes created by the same impulses that create excitation. The problem of inhibition has been submitted to careful analysis by Gasser (1935b; 1937a, b, c; 1938) who has suggested several diagrams accounting for different types of the phenomenon. Two elementary processes are considered: (1) rise in threshold of the neurons due to summation of subnormality; 2) lowering of the stimulating value of a synchronous volley of impulses by its fractionation into two volleys delivered at an interval longer than the effective period of summation of impulses arriving at different synapses.

Since the motoneurons and presumably all other neurons work at threshold, there is no doubt that either of the two processes will cause a deficit of response (inhibition). Several instances have been mentioned in this article as well as in previous papers, in which it was necessary to attribute the absence of response of ocular motoneurons to reduction or cessation of internuncial activity (Fig. 7, 13 to 22); and the diagrams in Figs. 12, I, and 13 explain how a closed chain of neurons including only a few links may act as an inhibitory mechanism. Summation of subnormality, however, will lead to the production of rhythm (Figs. 10 and 11) rather than to sustained inhibition, unless it is produced and maintained in cells which are common links of antagonistic chains of neurons.

The diagram suggested by Gasser (1938c) which is reproduced in Fig. 12, II, includes a link of this type in cell *b*; subnormality of that cell will allow activation of cell *E* or cell *F*, but not a simultaneous activation of both.

A similar linkage between paths  $A_1$  and  $A_2$  (Fig. 12, I) would explain the reciprocal exclusion of the appendages of vestibular nystagmus, and the same type of linkage between fibers  $f$  and  $f_i$  (Fig. 13) would explain the initial relaxation of the antagonist, which accompanies the initial contraction of the agonist in certain forms of nystagmus. The existence of an additional linkage ensuring reciprocal innervation is likely, because as previously mentioned, destruction of certain internuncial nuclei may abolish reciprocal innervation and cause co-contraction without abolishing rhythm.

Inhibition through the subnormality of cell  $b$  (Fig. 12, II) is very different from inhibition produced by a Wedensky block (Lucas, 1917, Fig. 22). Under certain conditions increase in the frequency of a train of impulses in nerve establishes the Wedensky block; and once established, the block is impassable for any impulse.\* Subnormality, on the contrary, produces a block for weak stimuli only, and no matter how strong the subnormality may be, it will be "broken through" if the stimulus is strengthened (Fig. 10, 15).

In principle, then, the problem of inhibition does not offer insurmountable obstacles, and the fact that it is due to excitation of certain neurons explains the similarity found by Sherrington (1925) and by Eccles and Sherrington (1931c) between c.e.s. and c.i.s. Inhibition must have all the properties of excitation, i.e., recruitment, subliminal fringe, etc., the only difference being that inhibition does not set up motor responses. Furthermore, inhibition must be maintained chiefly by internuncial bombardment, but other factors (cf. Dusser de Barenne and McCulloch, 1937; Dusser de Barenne, McCulloch, and Nims, 1937; Gerard, 1936a) may also become operative under given conditions.

The difficulties in the explanation of reciprocal inhibition appear when an attempt is made to identify the anatomical mechanisms, because inhibition by fractionation of synchronous volleys of impulses arriving at different synapses demands that excitation of some cells be brought about through pathways insuring a perfect synchronism of the arrival of impulses, despite the causes for the temporal dispersions responsible for the statistically constant bombardment observed during facilitation (cf. above, sub  $a$ ). The timing of the arrival of the impulses to the neurons responsible for inhibition must indeed be accurate. Fig. 14 reproduces records of an experiment in which the stimulating value of a synchronous volley of impulses was reduced by dividing it into two volleys delivered at variable intervals.

The diagram at the top explains the conditions of the experiment (cf. 1935c, Fig. 2). An F shock ( $F_i$ ) capable of firing fibers  $f_1$  and  $f_2$  (records 1, 5, 7) or  $f_1$ ,  $f_2$ , and  $f_3$  (9) was preceded by a smaller F shock ( $F_c$ ) capable of firing only fiber  $f_1$  (record 4). The conditioning shock was weak so that the  $f_c$  volley was not perfectly synchronous, which caused an apparent increase of the duration of the period of summation of the impulses delivered at neighboring synapses (cf. records 6 and 7). Nevertheless, there was an interval between

\* Several convincing reasons why a Wedensky block cannot be considered as the elementary mechanism underlying inhibition were given by Fulton (1926).

shocks (records 3 and 10) during which the response to  $F_i$  was clearly diminished. This interval was short, because the bombardment through internuncial cells  $i_i$  started by shock  $F_c$  caused the arrival to the motor nucleus of impulses which summated with the  $F_i$  impulses and gave rise to a facilitated response (records 2 and 8).

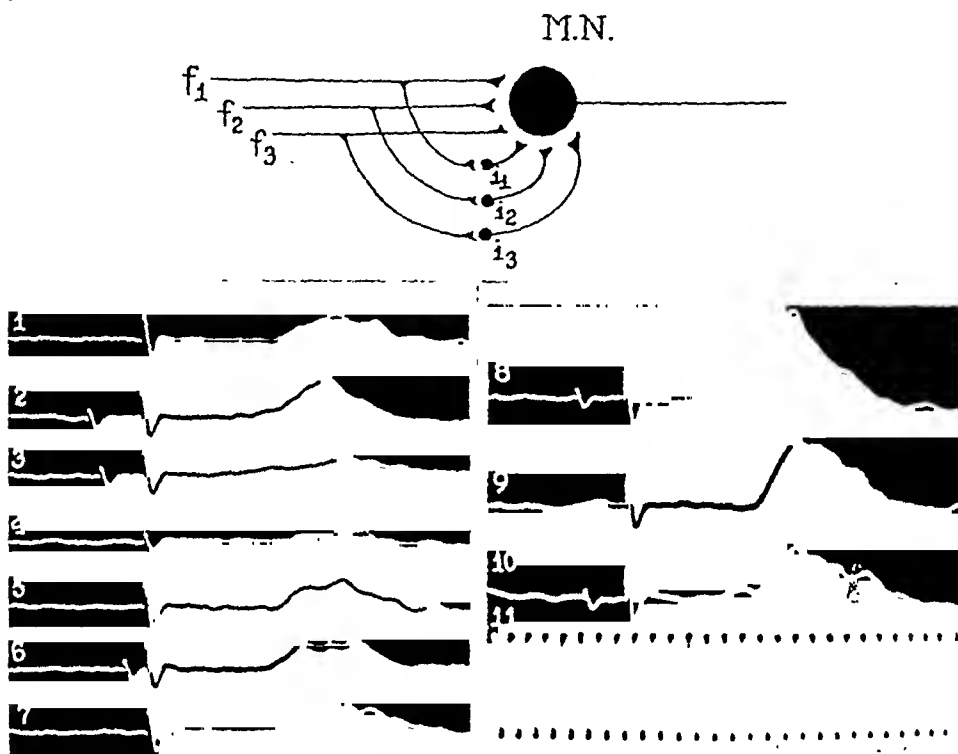


FIG. 14. Oculomotor preparation; responses recorded from the trochlear nerve (6-20-37). Stimulating electrodes on the floor of the fourth ventricle. The conditioning shock had the same strength in both series of records. The response to it in isolation is shown in record 4. The testing shock was 220 per cent stronger than the conditioning shock in records 1 to 7, and 300 per cent stronger in records 8 to 10. 1, 5, 7 and 9, responses to the testing shock in isolation. Note that in records 2 and 8 the response to the testing shock is facilitated; it is depressed in records 3 and 10 but is unaltered in record 6. 11, timing film (5000 cycles per second).

The existence of synchronizing mechanisms has been mentioned in previous paragraphs (p. 226). It is, however, not improbable that future research will lead to the discovery of still other, as yet unknown, synchronizing factors and of other agencies capable of maintaining inhibition.\* Synchronization of

\* Observations made on peripheral nerve (1938a) suggest that subliminal stimulation may play a role in the maintenance of inhibition. When a train of subliminal shocks is delivered to a nerve, each shock is followed by a period of local summation and a period of postcathodal depression, but the duration of the period of summation diminishes with each successive shock of the train, at the same time that the depth of the postcathodal

a large number of elements is a prominent characteristic of the activity of the cerebral cortex (cf. Bishop and O'Leary, 1936; Bishop, 1936). Gerard (1935a, b) has made a thorough analysis of the various factors, which in addition to the play of nerve impulses on neurons may be operative in modifying cortical rhythms. They belong into the class of enduring changes and therefore lie beyond the scope of the present paper (cf. above, parag. a).

### SUMMARY

An attempt is made to correlate data on the anatomy of the central nervous system with the results of physiological experiments.

The nervous system is composed of an exceedingly large number of interlacing pathways, which offer numerous opportunities for the conduction of impulses into divergent paths; but during activity it becomes fractionated into a group of active and another group of inactive neurons. The active neurons are arranged in convergent chains of relatively simple composition, which may be called the multiple (*M*, Fig. 2) and the closed chain (*C*, Fig. 2) through which impulses circulate. The fractionation is attributable to the fact that stimulation of a neuron requires the activation within a short period of time, which for the motoneurons is less than 0.3 msec., of several synapses having a determined spatial distribution on the neuron. The rigidity of the conditions necessary for the effective summation of impulses delivered to synaptic junctions is such that the impulses circulating through the active chains, despite their being very numerous, remain subliminal for the neurons of the inactive group.

Impulses circulating through the chains of neurons of the internuncial system create a statistically constant stimulus of motoneurons and internuncials, as both classes of neurons are submitted to a constant bombardment by impulses being delivered at their synapses. The neurons respond rhythmically at a rate dependent upon the strength of the bombardment and the rate of their recovery.

The multiple chain of neurons (*M*, Fig. 2) is the elementary unit of transmission; it supersedes the classical reflex arc with a fixed number of synapses. The rate at which a multiple chain may transmit impulses depends upon the number of neurons it contains; the greater the number of links, the lower being the minimal rate.

The closed chain of neurons (*C*, Fig. 2) may play different roles according to the number of links that it contains. If the number is small, activation of the chain may result in inhibition, but if the number of links is large enough it may result in sustained facilitation or discharge. It is indicated that after-discharge does not necessarily require autochthonous activity of closed chains of neurons; after-discharge must rather be interpreted as an especial

phenomenon which should take place during synaptic transmission, in the high subnormal threshold in the periods between stimuli, and then be accessible only to strong stimuli constituted by the absolutely synchronous arrival of several impulses.

case of reflex reversal, maintained by closed chains of neurons which keep the constant stream of impulses that have arrived from the periphery or from other centers within channels opened by the intercurrent stimulation.

The participation of the internuncial system in the establishment of reflex reactions is explained in some detail on the basis of diagrams designed to account for the production of vestibular nystagmus.

The elementary mechanisms underlying inhibition are discussed.

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# LOCALIZATION OF CEREBRAL LESIONS BY ELECTRO-ENCEPHALOGRAPHY\*

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## I. INTRODUCTION

A SURPRISINGLY high percentage of lesions of the cerebrum, particularly tumors, can be accurately localized by recording the alterations in the electroencephalogram. Unlike the clinical manifestations of cerebral disease, the electrical changes which accompany lesions in the so-called "silent" areas are as definite and as localizable as those arising from lesions in any other portion of the cerebral cortex. The method is simple of application, once the apparatus is available, and examination does not require the attention or the active cooperation of the patient. Since it is not a tiring or painful experience, and since it in no way endangers the patient's life or disturbs his physical condition, the advantages of the method are obvious. The records, moreover, are graphic, objective and impersonal. Apart from these clinical advantages in diagnosis and localization of cerebral lesions the results are of sufficient general interest to invite the attention of neurophysiologists.

## METHODS AND APPARATUS

The apparatus used consisted of three separate amplifying channels composed of resistance-capacity coupled amplifiers working into an ink writing oscillograph. The principal characteristics of the apparatus are: (1) Time constant of amplifiers 0.8 second; (2) Sensitivity as generally used such that 30 microvolts produces deflection of 1 mm. of inked line on moving tape; (3) Ink writer capable of recording any frequency from 0 to 170 cycles per sec. with slightly diminishing sensitivity above 100 cycles.

In operation all amplifiers are grounded together at one point and this point is attached routinely at the vertex, the grid leads of the several channels being attached by small silver plates about 1 cm. in diameter at any desired points on the cranium. When an area of interest is located, the central ground is shifted over or near this point and the grid leads grouped in radiating fashion about it at shorter distances from this center than before.

The deflection of the writing arm represents, then, the total voltage between the center of the system (usually at vertex) and the silver disc to which the respective grid lead is attached. And while the terms "frontal" lead and "occipital" lead are commonly employed in the following descriptions, it is understood that the deflections referred to are not due to potentials about the silver disc in question but represent the total potentials between the disc (in the frontal or occipital region as the case may be) and the grounded centre of the amplifying systems either at the vertex or over the point of interest. The terms "different" and "indifferent" as applied to such electrodes are false and misleading and the philosophy associated with the use of these terms has resulted in many unfortunate misconceptions.

## *Electro-encephalogram*

The electrical phenomena which arise from the brain in both normal and pathological conditions and are detectable at the scalp may be roughly classed as periodic (rhythmic) and aperiodic (irregular). While it is possible that the

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brain might under some circumstances give off waves of almost any frequency between one cycle in five or more seconds and 35 cycles per sec. or higher, there seem to be certain frequency bands into which most of these waves fall, and certain frequencies which are not often seen. The common frequency bands in the encephalographic spectrum are roughly:

- |                          |                                |
|--------------------------|--------------------------------|
| (a) below 1 per second   | } pathological or during sleep |
| (b) 1 to 3 per second    |                                |
| (c) 6 per second         |                                |
| (d) 7.5 to 11 per second | } normal                       |
| (e) 14 per second        |                                |
| (f) 18 to 35 per second  |                                |

Fig. 1 represents a rough estimate of the brain wave spectrum obtained from the electro-encephalograms of a considerable number of our patients.

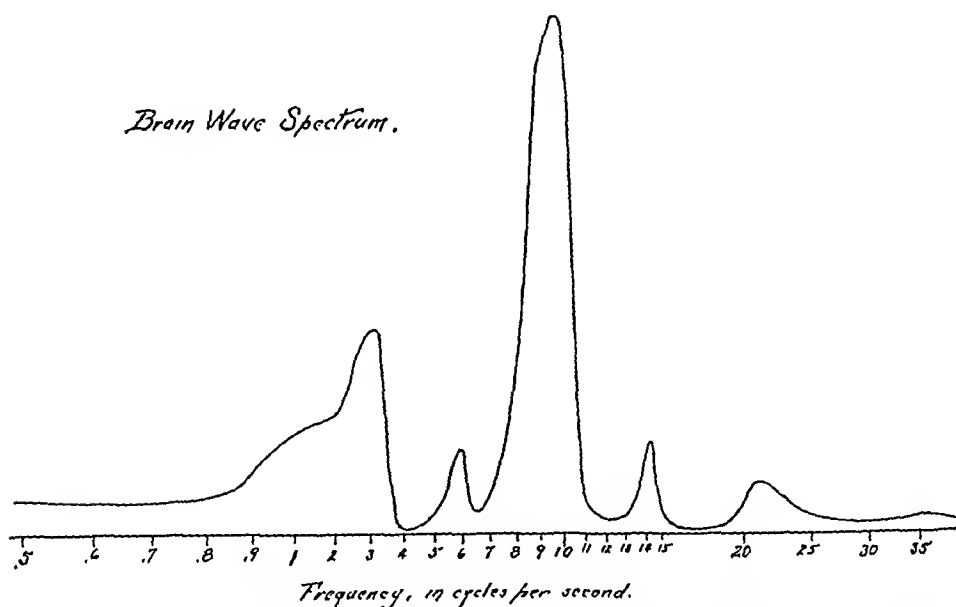


FIG. 1. Showing relative incidence of human brain wave frequencies in a group containing about 50 per cent of patients with some cerebral lesion.

While the ordinates of this curve represent the number of times of appearance of waves of any one frequency, it must be emphasized that the curve is estimated since no adequate quantitative compilations have yet been made. Others will doubtless place much less stress upon the three- and six-cycle bands, which have been here augmented by a considerable experience with patients subject to minor epileptic seizures. It should be noted that the valleys in the picture are perhaps just as significant as the peaks; a frequency of 4 per sec. is uncommon and the appearance of 7 per sec. rhythm is not relatively common. While many higher frequencies than those here represented are

encountered, their nature and significance are not sufficiently understood for discussion.

Roughly speaking, those frequencies which lie between 8 and 40 per sec. seem to be "normal" and healthy, although their absence or their relative amounts when present may be of considerable pathological significance. Those frequencies which lie below 8 per sec. appear to be pathological and to accompany abnormal conditions, with the possible exception of sleep in which slow waves are seen<sup>1,2,3</sup> but in which their frequency is seldom maintained long enough to count at any definite figure.

The aperiodic or irregular phenomena are more difficult to describe, and are composed largely of transients, which die out too quickly to be counted at any definite frequency, of transitional and rapidly changing forms and also of more or less definite figures such as "spikes" and "saw-tooth" forms which probably represent relatively isolated cortical discharges. These spikes, at least when present in considerable numbers, point strongly to an abnormal condition although cases with moderate numbers of isolated spikes are not uncommonly seen in which confirmatory evidence of pathology has not been found.

Swings of potential not sufficiently regular or sinusoidal to merit the term of waves are common in the very low frequency region where they may appear quite irregularly or fairly regularly at rates of from one in 10 seconds to perhaps one in 2 seconds. Such swings are seen in sleep and in many pathological conditions. They are also seen in anesthetized subjects and in those with increased intracranial pressure<sup>4</sup>. Their presence in connection with tumors is not uncommon and while of probable value in suggesting such lesions they may not always have localizing significance.

Tumors and some other lesions usually give rise to slow waves and sometimes spikes, which undoubtedly arise from the disturbed tissue around the tumor<sup>5</sup>. These electrical phenomena may be quite sharply localized and by them the position of the tumor may often be rather well determined. Walter<sup>6</sup> has presented several cases in which such localization has been made by the presence of 3 per sec. waves which he has called delta waves. This particular frequency, although often seen about tumors, is, however, not necessarily indicative of tumor or other irritative lesions but seems to be a rather fundamental wave-pattern for children with minor epilepsy<sup>7</sup>. Most of the waves which are seen about tumors and which might well be all classed as delta waves range in frequency from about 0.5 per sec. to about 4.5 or 5 per sec., the most common frequency being 1 or 2 per sec. Such waves at frequencies greater than 3.5 per sec. are rare.

## II. LOCALIZING PHENOMENA

In the 11 cases presented here, 8 instances of cerebral tumor and 3 of cerebral scars, the findings in the electro-encephalogram which indicated the presence of a localized cerebral lesion were: (a) regular waves with a frequency of one to 3 per sec.; (b) very slow swings in potential varying from

one in five to one in two seconds; (c) irregular sharp or saw-tooth spikes; (d) electrical phenomena characteristic of localized convulsive seizures; and (e) absence of normal alpha waves.

(a) The most common localized electrical phenomena indicative of underlying pathology were waves occurring at the frequency of one-half to three cycles per second. Waves of around 3 per sec., as has been pointed out, are characteristic of children suffering from petit mal. In such instances, however, they are not localized. In the cases presented in this paper these waves arose from a localized area referable to the lesion. They were present in seven of the eleven cases (Nos. 1, 2, 4, 7, 8, 10 and 11). In 3 of these cases (Nos. 4, 8 and 11) their frequency was about one per sec.; in 3 (Nos. 2, 7 and 10) it was 2 per sec.; and in one (No. 1) it was 3 per sec. It is obvious that the slower frequencies, one or two per sec., are the most common. In all instances these waves were most marked and most constant at or very near the site of the lesion. In 2 cases (Nos. 8 and 10) they were confined to that region. In 2 cases (Nos. 7 and 11) and possibly a third (No. 4) they were less constant and of smaller amplitude in other portions of the same hemisphere. As these waves obtained at a distance from the lesions were nearly in phase with the more prominent waves, it seemed likely that they were propagated from the region of the lesion. In some cases records obtained from two points on opposite sides of the region of greatest intensity would give waves which were 180° out of phase with each other (see Case No. 1). In two instances (Nos. 1 and 2) synchronous waves, less constant and of lower amplitude, could be obtained from the same lobe of the other hemisphere.

(b) In 4 cases (Nos. 1, 3, 9 and 11) very slow but regular swings in potential ranging from once in five seconds to once in two seconds could be obtained. In Case 1, in which there was a well circumscribed astrocytoma of the left frontal lobe, such waves were obtained from both frontal lobes. The same was true of Case 11, but here necropsy revealed that the tumor had spread through the corpus callosum to involve the other frontal lobe. In Cases 3 and 9, instances of a superficial cortical scar and traumatic subarachnoid cyst, and of a cystic glioma of the left occipital lobe respectively, this phenomenon was limited to the site of the lesion.

(c) Sharp, sudden alterations in potential giving rise to spikes may occur singly, irregularly, or regularly in brief runs. Such spikes as previously noted, are apparently significant only when present in considerable numbers. The runs are particularly worthy of note. Such spikes were prevalent in 4 cases (Nos. 1, 5, 6 and 7). In Case 5, a meningioma of the superior right precentral region, and in Case 6, a traumatic scar in the right frontal region, the spikes were localized to the area of the lesion. In Case 7, a meningioma of the postero-inferior part of the left frontal lobe, a few asynchronous spikes were obtained from the opposite frontal lobe and some spikes of lower amplitude but synchronous with those from the left frontal region were obtained from other parts of the same hemisphere. In Case 1, a circumscribed left frontal astrocytoma, a few asynchronous spikes were obtained from the opposite right frontal region.

(d) In one case (No. 3) in which there was extensive scarring of the dura mater, arachnoid and pia mater over the right frontal lobe associated clinically with generalized convulsive seizures, electrical phenomena characteristic of those obtained from individuals suffering from localized convulsive seizures were obtained only from the right frontal region. These did not spread to any other region and were not associated with any objective or subjective evi-

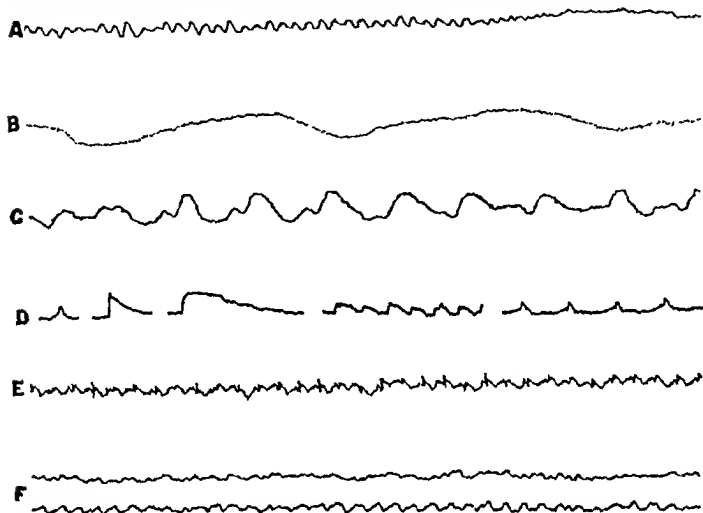


FIG 2 Showing (except line A) the electro-encephalographic configurations indicative of localized cerebral pathology. Line A is a normal tracing starting with the eyes closed, showing a fairly prominent alpha wave which disappears at the end of the line where the eyes are opened. Line B shows slow waves having a frequency of 0.5 per sec. Line C shows 2 per sec. delta waves. Line D shows cusp-shaped and saw-tooth spikes, singly and in runs. Line E shows the electrical manifestation of a localized epileptic seizure. Lines F show the absence of alpha waves (upper tracing) from the occipital lead on the side of a tumor and simultaneously the presence of alpha waves (lower tracing) in the occipital lead from the unaffected side. All these tracings are to the same scale in voltage and in time.

dence of a seizure. This characteristic electrical phenomenon is the typical "wave and spike pattern" which has come to be looked upon as pathognomonic of minor epilepsy. In this case the total deflection of the localized seizure was around 40 microvolts and the duration of the seizure one to two minutes (in contrast to the usual petit mal deflection of around 200 microvolts with a seizure duration of about 10 to 15 seconds).

(e) In 2 cases (Nos. 2 and 9) an absence of the normal (8 to 10 per sec.) alpha rhythm was obtained. In Case 2 this absence was found only on the

side of the lesion—a large localized traumatic cerebral atrophy extending from the cortex to the ventricle in the left parietal region, the surface of which had been surgically removed. In Case 9, a cystic glioma of the left occipital lobe, the alpha rhythm was absent from both occipital lobes, whereas localizing slow shifts of potential were present (left side). However, these electro-encephalograms were obtained following attempted ventriculography during which the cyst on the left side was evacuated, while on the right side, because of an anatomical abnormality, the needle was inserted down the calcarine fissure resulting in a temporary left homonymous hemianopsia and a permanent small paracentral scotoma.

The features which have been noted above as indicative of cerebral lesions are illustrated in Fig. 2, which is a composite made up of episodes clipped from various records. This figure shows the principal electro-encephalographic configurations which we believe are indicative directly or indirectly of cortical lesions.

### III. DISCUSSION

In all of these 11 cases the pathology has been determined either at operation or autopsy, or has been demonstrated by pneumoencephalography. The location of the pathology and the approximate localization indicated by electro-encephalography have been in substantial agreement. In one patient with a large brain tumor (Case 11) only small waves indicating a lesion were obtained. This patient had had a subtemporal decompression which may have reduced the pressure on the cortex. A total of 13 patients having cerebral lesions later confirmed by operation, autopsy or both, have been examined by electro-encephalography in the last twelve months, from which the above 11 cases have been chosen. All of these have shown some evidence suggestive of an intracranial lesion. No attempt has yet been made to evaluate the electrical possibilities in posterior fossa lesions or in pituitary disorders.

Waves having frequencies from 0.5 to 3 per sec. which are sensibly equidistant from peak to peak for at least five cycles seem to be quite characteristic of tumors but are also seen with other types of localized pathology. With the exception of waves at about 3 per sec. commonly seen with minor epilepsy, but not so distinctly localized or lateralized as with tumors, such waves have always, when obtained from patients while awake, indicated gross cerebral pathology. It should be noted that waves of this frequency can be simulated by rhythmic eye movements or rhythmic movements of the eyelids but these artifacts appear only in the frontal leads and are equal and simultaneous on the two slides.

The very slow swings—less than 0.5 per sec.—are found in many pathological conditions, particularly the chronic degenerative diseases and chronic encephalitis. While such slow shifts of potential are seen in connection with cerebral tumors they are not peculiar to them. In most conditions they appeared most commonly and prominently from the frontal lobes. Only when they are localized to one area of the head, as in Cases 3 and 9, can they be considered to have any localizing value.

The records obtained during sleep may at times be confusing. In sleep many slow transitional forms are seen. Occasionally quite regular runs are present, often around one per sec. It should be noted whether the patient is sleeping and whether such waves are localized to any single area. Great care must be exercised in the interpretation of the various signs. This is particularly true in the matter of spikes; an occasional isolated spike carries little weight, but when seen in considerable numbers or in series they seem to imply an abnormal cortical discharge.

The absence of alpha waves from the occipital leads or their gross inequality in corresponding areas on the two sides should arouse suspicion and is at times corroborating evidence but at the present time does not in itself carry much weight. The appearance of the electrical manifestations typical of localized epileptic seizures is rare. They probably have great localizing and diagnostic importance. Theoretically, few waves should be obtained over areas where the cortex is atrophic or where there is a cyst. We recall a case in which considerable activity was present in frontal, temporal and occipital leads and appeared of almost the same form in these three leads simultaneously. Operation revealed a large porencephalic cyst in the posterior frontal region, over which the cortex was so thin and gelatinous that it probably had little, if any, function. It seems probable that most of the electrical activity was here transmitted up from the neighboring intact regions.

It is perhaps unnecessary to emphasize that abnormal waves, especially those from 0.5 to 3 per sec., come in trains or spindles, and that their amplitude varies from time to time. Because of this, multiple simultaneous recording from several areas of the head is essential for any certainty of localization. It is felt that while the method of electro-encephalography is of necessity somewhat indefinite in the outlining of cerebral tumors and other lesions, it does, nevertheless, compare favorably in this regard with many of the methods now in use, and that there are many lesions which it is possible to indicate more or less definitely by this means where other methods give only negative findings. In view of these possibilities it seems likely that electro-encephalography will become an essential adjunct in the localization of intracranial lesions.

#### IV. SUMMARY

Electro-encephalography presents an easily applied, non-tiring and non-traumatizing, relatively simple means of localizing many cerebral lesions, particularly with reference to tumors and other focal lesions. Intracranial lesions are indicated and may usually be localized by the following electro-encephalographic phenomena:

1. Very slow swings, 1 to 2 in 5 seconds.
2. Slow waves from  $\frac{1}{2}$  to 3 per sec.
3. Spikes and saw-tooth forms.
4. Electrical manifestations of localized epileptic seizures.
5. Absence of or marked difference in the alpha rhythm on the two sides.
6. Marked diminution or localized absence of electrical activity.



Eleven cases are presented in all of which the lesions have been localized more or less accurately by this method and which collectively show most of the above features. In 8 of these cases tumors were present, in 2 there were cerebral scars which had resulted from trauma, and in one there was a marked scarring of the meninges. All have been confirmed by roentgenograms, operation or necropsy.

It is suggested that the electro-encephalographic method will become a valuable adjunct in the diagnosis and localization of intracranial lesions.

### CASE REPORTS

CASE 1. (C. R. M., No. 177797), a white male, 36 years of age, was by referred Dr. Harold Evans of Davenport, Iowa. He was well until seven years prior to admission on



FIG. 3. Case 1. This pneumo-encephalogram shows the anterior portion of the left lateral ventricle displaced downward with a large filling defect in the posterior part of the displaced area which was caused by a nodule of tumor within the lateral ventricle.

June 23, 1937. The onset of his present illness was with a right-sided convulsive seizure. Subsequently he had many such attacks and some generalized seizures in all of which however, he lost consciousness. Following many of these attacks he experienced a temporary difficulty in speaking and weakness of his right extremities. During the last year he had developed increasing difficulty in speaking and slight weakness in the right upper extremity.

Examination revealed only a definite motor aphasic defect and some awkwardness in rapid movement of the right hand. Pneumo-encephalography indicated a large tumor in the left posterior frontal region (Fig. 3).

The electro-encephalogram showed very slow negative swings in the frontal leads only. These were irregular but often came at a rate of about one in 5 seconds. Three per second waves, large and regular, were seen in the lead from the mid-line of the frontal region, propagated slightly into the right frontal region, and were absent in the occipital areas

(Fig 4). Here, as in all subsequent figures, the circle represents the common point of the amplifying systems, the dots represent the points at which the individual amplifiers are applied. When the center point of the amplifying system was shifted over the left frontal lobe and the amplifiers spread out fanwise as in the sketch, Fig 4B, these waves were seen in all three leads, largest in the anterior lead, smaller toward the vertex, with a gradual phase shift around the central point so that the voltage in the lead towards the temporal region is  $180^\circ$  out of phase with the voltage in the lead towards the midline frontal region. This is well shown in Fig 4 and suggests that the source of these waves lies somewhat anterior to the center point of the amplifying systems. Sawtooth spikes were seen in the lead from the left frontal region. These were irregular but quite numerous in this area and

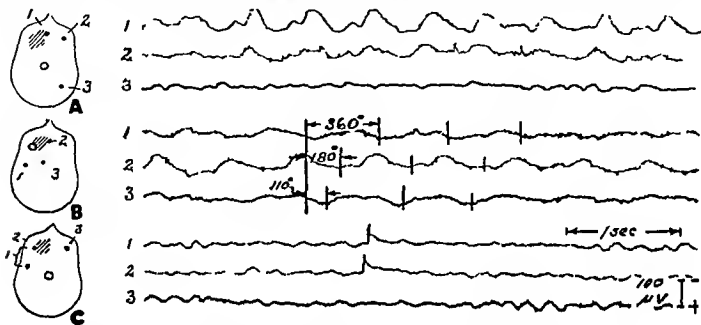


FIG 4 Case 1 Delta waves at A<sub>1</sub> arising from the mesial aspect of a tumor

seemed to come in showers. Occasional similar spikes, much smaller and much less numerous, were seen from the right frontal area. Some spikes from the left frontal area are shown in Fig 4C. (In Fig 4C, lead 1 records the voltage between the left temporal and left frontal regions, leads 2 and 3 between the left and right frontal regions respectively and the vertex.) From this electroencephalogram it was concluded that there was a lesion lying in the mid portion of the left frontal lobe.

Subsequently, on June 29, 1937, the patient was operated upon and a large, well circumscribed benign glioma (astrocytoma) which measured 7 cm. in diameter on the surface was removed from the substance of the left frontal lobe. The tumor lay 1 cm. medial to the superior longitudinal fissure, 1 cm. anterior to the precentral vein and 2 cm. above the Sylvian vessels. The tumor was cone shaped, the base presenting on the surface of the brain, the apex extending inward to the lateral ventricle, with a small nodule of tumor actually lying within the anterior horn of the ventricle. The patient made an uneventful recovery.

CASE 2 (H. J. P., No. 143696), a boy 19 years of age was referred by Dr. Albert H. Montgomery of Chicago. This boy was well until the age of 5 when he sustained a compound depressed fracture of the skull in the left posterior parietal region. This was treated surgically and the boy was quite well, except for some slight weakness of the right extremities, until the age of 13 when he began to suffer from convulsive seizures involving the right arm only. These attacks were preceded by an indescribable visual aura. On only two occasions did the patient lose consciousness. The attacks occurred about 3 times a week in spite of the administration of phenobarbital and bromides.

Examination showed a large soft pulsating defect in the bone of the left parietal area. There was some spasticity of the right arm and leg and some difficulty in making rapid movements. Sensory perception was slightly reduced on the right side and stereognosis in the right hand grossly impaired. Babinski's sign was present on the right. Pneumoencephalogram revealed a large dilatation of the left lateral ventricle at the genu with considerable regional atrophy of the brain.

At operation on January 24, 1936 the cortex in the affected area was found to be avascu-

lar and gelatinous and was very thin, with a much dilated genu of the ventricle immediately beneath. All of the cortex overlying the ventricular dilatation was removed. Since then there has been no recurrence of the convulsions.

After 4 months he was readmitted for further study. Electro-encephalography done at that time revealed an absence of alpha waves on the left side and their definite presence on the normal side. (This finding is directly opposed to that of Lemere<sup>9</sup> who found alpha waves absent on the unaffected side and present on the side of a lesion.) Good runs of waves at about 2 per sec. were seen especially in the left frontal lead but also to a lesser extent in the right frontal, pointing to a source of irritation somewhat to the left and forward of the vertex. This is seen in Fig. 5A. In Fig. 5B are seen 3 simultaneous tracings showing 2 per sec. waves in the left frontal, 8 per sec. waves in the right occipital and nothing definitely periodic in the left occipital lead. The cause of the 2 per sec. waves is here most probably some cicatricial contraction at the anterior end of the cortical defect which has been indicated by shading in the sketch in Fig. 5.

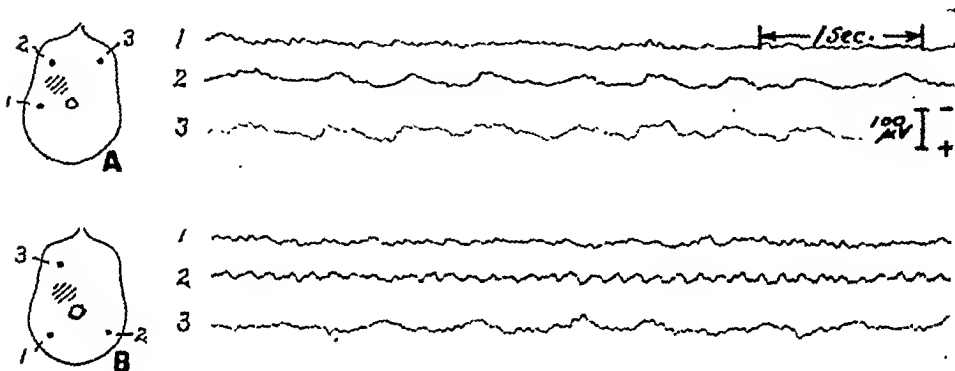


FIG. 5. Case 2. Delta wave at A<sub>2</sub> and B<sub>2</sub>, arising from the anterior aspect of a scar, and at B<sub>1</sub> absence of alpha waves on the side of the lesion.

CASE 3. (L. B., No. 137071), male, 25 years of age, was referred by Dr. L. E. Dupes of Hobart, Indiana. He was perfectly well until the age of twenty-one years when he suffered from a nocturnal generalized convulsion. During the following four years he had about six such seizures. Recently severe headaches had developed. Just prior to his admission January 28, 1937, he suffered from a series of attacks in which he lost consciousness but had no convulsion. Examination revealed a bony prominence over the right frontal sinus. There was an anosmia on the right side, a slight left lower facial weakness, and the left platysma myoides did not contract. There was a questionable sign of Babinski on the left side. Roentgenograms of the skull revealed a large osteoma in the right frontal sinus with several knob-like protrusions of the osteoma through the inner table of the skull.

Electro-encephalography revealed slow waves having a frequency of one every two seconds localized to the right frontal lobe, and localized epileptic seizures in this area which did not spread to other areas and did not produce any clinical evidence of a seizure. Indeed, he would talk and answer questions during a seizure and denied any knowledge that anything unusual was occurring. These seizures occurred also while he was asleep and during sleep also there was no clinical evidence of an attack. The voltage associated with these attacks was of the order of about 40 microvolts total deflection, and the attacks lasted about one minute, that is, considerably longer than most minor attacks.

These slow waves are shown in Fig. 6A where they are seen with tracings taken simultaneously from other areas. At B is seen the typical manifestation of a localized epileptic seizure. It was obtained only from the right frontal region. The tracing showing this seizure has been enlarged two diameters at C to show more clearly the typical "hump and spike" formation.

The patient was operated upon on February 2, 1937. A right frontal osteoplastic flap was reflected and a large osteoma was removed from the frontal sinus. It possessed five knob-like protrusions which penetrated the inner table of the skull and the dura mater

and were embedded in the brain. The dura mater had of necessity been opened in removing these bony knobs. It was firmly adherent to the underlying arachnoid membrane throughout all of the exposed area, i.e., over the right pre frontal area. There was extensive fibroblastic proliferation involving all of the meninges in this region. How far beyond the operative field this process extended could not be stated. It appeared likely that it was the result of a low grade infection that had penetrated the subdural space from the frontal sinus along these bony protrusions. There has been no recurrence of the convulsive seizures since the operation. Phenobarbital has been taken regularly.

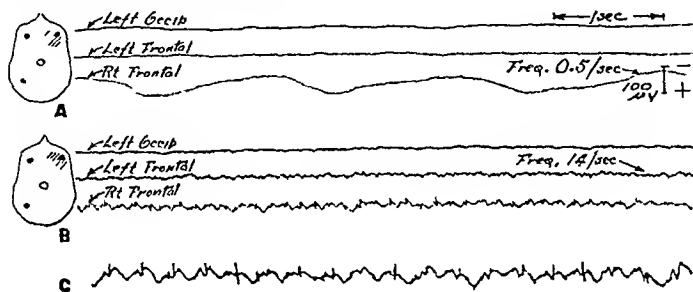


FIG 6 Case 3 Right frontal lead over meningeal scarring shows at A,  $\frac{1}{2}$  per sec delta waves and at B, subclinical epileptic seizure pattern, localized to this area. At C, seizure pattern enlarged two diameters.

CASE 4 (J O, No 155035), a male, 51 years of age, was admitted to the University of Chicago Clinics on July 6, 1936 complaining of attacks which had been present for three months. These attacks began with a bad taste in his mouth, occasionally the smelling of an unpleasant odor, he would then become nauseated and his hands would shake. He did not lose consciousness. On examination the only findings were a marked euphoria and a persistent attempt to joke and make witty remarks. The visual fields were normal. A ventriculogram was made which indicated a tumor deep in the substance of the right temporal lobe.

He was operated upon on July 11, 1936. An extensive infiltrating glioma was found deep in the right temporal lobe extending into the basal ganglia. The overlying cerebral cortex of almost all of the temporal lobe was removed and a large part of the glioma.

Electroencephalography was done about two months after the operation and as we were at that time looking only for changes in the alpha rhythm due to tumors, only occipital leads were taken. They show a wave having a frequency of slightly greater than

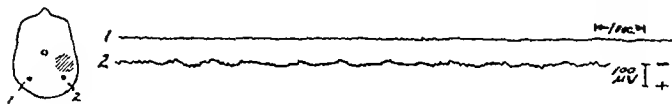


FIG 7 Case 4 Delta waves from posterior aspect of lesion, none from opposite (not involved) side.

1 per sec. in the right occipital area, in contrast to the left occipital region which shows nothing of this nature. Whether this wave, which may have been larger further forward, was caused by the remaining tumor or was due to some pathology resulting from the operation, is impossible to say. Small alpha waves are seen in both occipital leads, in the right superimposed on the one per second waves. These findings are seen in Fig. 7 which shows a section of the record taken in this case.

CASE 5. (P. H., No. 169364), a white female, 47 years of age, was referred by Dr. A. G. Miller of Hobart, Indiana. Since the age of 39 she had suffered from weakness and numbness of the left lower extremity which had begun in the toes and grown progressively more severe and extensive. For the past 7 years she had suffered from convulsive seizures limited to the left upper extremity until the last year when the attacks had become generalized and were accompanied by loss of consciousness. Examination revealed considerable weakness and spasticity of the left lower extremity. She was unable to move the toes or ankle voluntarily and walked with a hemiplegic limp. There was no disturbance in the cranial nerves. Sensation was intact. In the left upper extremity there was moderate weakness of movement at the shoulder and elbow and some slight spasticity. Rapid alternating movements were impossible in this extremity. There was slight atrophy of the musculature about the shoulder. Tendon reflexes were all increased on the left side, the abdominal reflexes were absent and Babinski's sign was present. Roentgenograms of the skull revealed no abnormality.

Electro-encephalography showed a large number of irregular discharges usually of a saw-tooth form, sometimes singly but sometimes so fast and regular as to give almost a sinusoidal appearance. These appeared in the right posterior frontal area and were localized to this region. There were no slow waves or delta waves. Fig. 8 shows two runs of these saw-tooth discharges both appearing in the right frontal lead.

At operation on March 18, 1937 a small parasagittal meningioma was found over the right central gyrus just lateral to the superior longitudinal sinus. It lay astride the central vein which was greatly engorged. The tumor was removed.

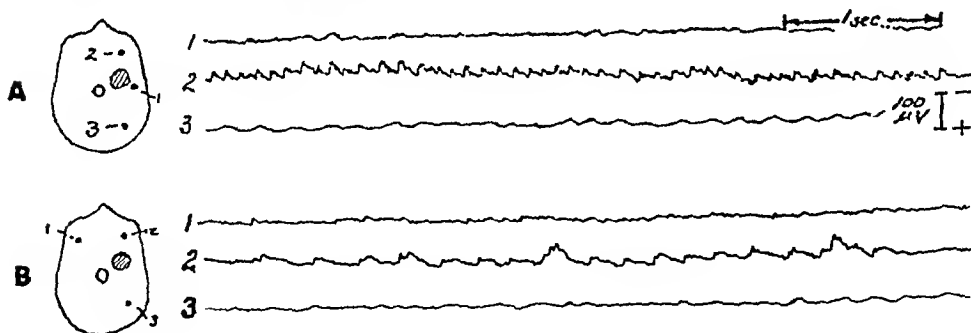


FIG. 8. Case 5. Saw tooth pattern,  $A_2$ , and  $B_2$ , in long runs, sharply localized to anterior aspect of small meningioma.

CASE 6. (J. S., No. 176916), male, 22 years of age, was admitted to the University of Chicago Clinics on July 2, 1937 complaining of "fainting spells" which began two years before. At the age of 2 years he had fallen from a third story window and sustained a severe deforming fracture of the skull as a result of which an irregular bony prominence had persisted in the frontal region. He was unconscious for a time following this accident and lost the power of speech for the succeeding 6 months. Since this accident movements of the right arm and leg had been weak and awkward and he was lethargic and mentally retarded, reaching only the fifth grade in school. At the age of 18 he was involved in an automobile accident in which he was thrown from the car into a snowbank but suffered no ill effects. When 20 years of age he suddenly lost consciousness without warning and for no apparent reason, and then developed a generalized convulsion which was so severe as to throw him out of bed. Since then these attacks have recurred about once every month. Examination revealed a bony ridge about 6 inches long running along the coronal suture and another

spherical elevation a short distance posterior to this ridge on the left. He was apathetic and responded slowly to all questions. At times he stammered and had difficulty in finding words. It was difficult to hold his attention and sensory examination was unsatisfactory. The right upper extremity was somewhat smaller than the left and, although there was no weakness, he was markedly awkward in all movements of this extremity and it did not swing as he walked. The tendon reflexes were all slightly hyperactive on the right side, the abdominal reflexes were absent on that side but Babinski's sign was not elicited. Roentgenograms of the skull revealed an extensive bony deformity along the coronal suture on

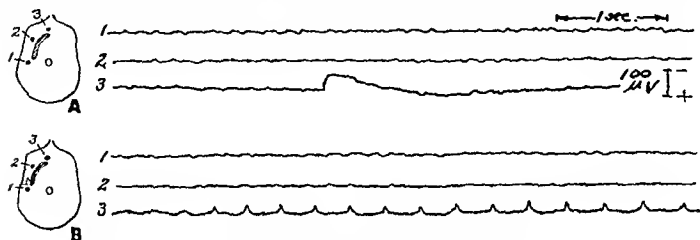


FIG. 9. Case 6. Cusp shaped spikes,  $B_3$ , sharply localized to the anterior end of a long cortical scar.

the left side and extending backward into the left parietal bone. Pneumo-encephalography revealed some enlargement of the left lateral ventricle and a large defect in the cerebrum beneath the bony deformity.

Electro-encephalography showed irregular spikes, mostly cusp-shaped, singly and in runs, rather sharply localized near the anterior end of the deformity of the left frontal bone. None was obtained from other areas. Fig. 9 shows a run of cusp-shaped spikes and a single more saw-toothed form obtained from this area.

CASE 7. (F. K., No. 185650), a white female, 49 years of age, was admitted to the University of Chicago Clinics on November 7, 1937 complaining of convulsions. These had begun in October, 1936 and she had suffered from seven such seizures. In these attacks she would suddenly and without warning lose consciousness, the face and jaw would be drawn to the right, all extremities becoming rigid, and she would froth at the mouth. Following

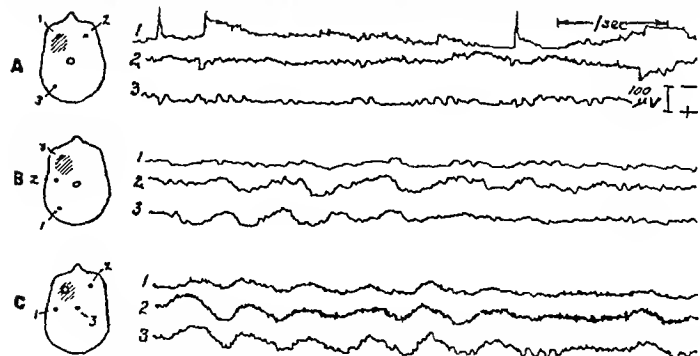


FIG. 10. Case 7. Delta waves from the neighborhood of a tumor at  $B_2$  and  $B_3$ .

each attack she would be unable to speak for from several hours to two days. Ever since the first convulsion there had been some persistent difficulty with speech. In addition to these major attacks there had been many minor seizures of short duration in which she did not lose consciousness but was wholly unable to speak, although she insisted that she knew what she wished to say. Since March, 1937, she had been unable to read and, although able to write, could not spell correctly. Examination revealed inability to form a coherent sentence including three simple words which were given to her, or to relate the contents of a single sentence read from the newspaper. Enunciation was very poor. There was a slight right lower facial weakness and a very slight weakness of the right upper extremity. Rapid



FIG. 11. Case 8. Large calcified oligodendroglioma in the medial portion of the left frontal lobe. In this ventriculogram the slightly dilated right ventricle which is normal in shape can be faintly seen. There is only a small amount of air in the left lateral ventricle, the anterior horn of which has been cut off and displaced backward. This ventricle communicates with a series of cysts in the superior part of the frontal lobe.

alternating movements were done less well by the right hand. All tendon reflexes were hyperactive on the right side. Babinski's sign was not present. The findings on lumbar puncture were normal. A pneumo-encephalogram revealed that the anterior horn of the left lateral ventricle was shifted slightly toward the right.

Electro-encephalography showed sharp spikes, most prominent and most frequent in the left frontal area. They were also seen in the left temporo-occipital and right frontal areas where they were rounded but synchronous with those in the left frontal area and probably transmitted from it. The right frontal area also showed a few sharp spikes which were not associated (synchronous) with anything seen elsewhere. Spindles or brief runs of regular waves of about 2 per sec. were seen in the left frontal and temporal leads, usually somewhat larger in the frontal. These waves were transmitted to other areas but were very small there, as is seen in the left occipital lead of Fig. 10. This figure shows at (A) spikes from the left frontal area, and (B) 2 per sec. waves from the left frontal and temporal areas, the temporal appearing to be somewhat slower, and at (C) the reference point has been shifted to the left frontal area, giving waves in all three leads. The fact that they are all in

phase and of nearly the same amplitude indicates that the reference point was in the vicinity of the disturbance.

At operation a meningioma about the size of a tennis ball was found lying in the inferior part of the posterior frontal region, its inferior margin about 3 cm. above and anterior to the central sulcus. Since operation phenobarbital has been administered and she has had no further convulsions and her speech has steadily improved.

CASE 8. (C. C., No. 185438), a white male, 53 years of age, was admitted on October 17, 1937 complaining of "fainting spells." In April, 1937, he had had his first generalized convulsion which occurred without warning and without any focal phenomenon. In May, 1937, 4 more such seizures occurred in one day. There were no more until September of that year when he began having them at frequent intervals. His wife had occasionally noted attacks of jerking of the right leg while the patient was in bed at night. On examination he was apathetic, disinterested in his surroundings, and paid no attention to his mail or the newspaper. He was quite unconcerned about his condition or the proposed operation

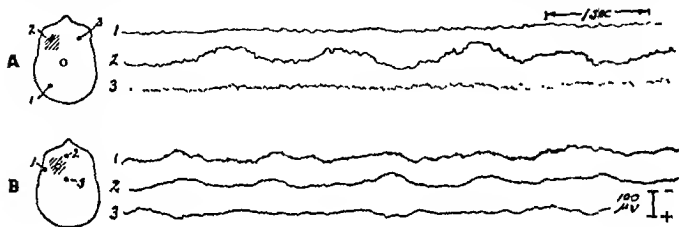


FIG. 12. Case 8. Delta waves over tumor, at A<sub>1</sub>.

and rarely spoke except in response to direct questions. There was, however, no demonstrable aphasia. There was a questionable weakness of the facial musculature on the right and of the right upper extremity. The tendon reflexes were somewhat more active on the right side. Babinski's sign was not present. Roentgenograms of the skull revealed a large area of calcification in the left posterior frontal region. Ventriculography indicated a tumor in the area of calcification containing a cystic cavity which communicated with the lateral ventricle. Fig. 11 shows this calcification and the distortion of the ventricle backward and downward by the tumor.

Electro-encephalography showed spectacular runs of waves of a frequency slightly less than one per second, almost continuous and sharply confined to the left frontal lobe. These are seen in Fig. 12, and at (B) the central point of the amplifying system has been placed on the left frontal area, the points to the individual amplifiers being grouped about it at a radius of about two inches. Waves are seen in all leads suggesting that their point of origin probably lies within the circle formed by these leads. From the phase relation and relative size of these waves, the direction of propagation was deduced to be from in front backwards (across the area from which voltages are picked up) and the source somewhat in front of the center point of the amplifying systems.

At operation on October 26, 1937 the surface of the cortex of the left frontal lobe showed definite... The anterior two-thirds of the frontal lobe was amputated and a large part of the tumor removed. It proved to be an oligodendroglioma.

CASE 9. (M. D., No. 459), a white female, 26 years of age, was referred by Dr. M. M. Hoeltgen of Chicago. She was admitted on September 27, 1937. For 10 years prior to admission she had repeatedly experienced brief attacks of flickering lights before her eyes. These were not lateralized. They were not associated with any other phenomenon until one year before admission when the seizures became more frequent and were associated with severe headaches, nausea and at times vomiting. Examination revealed a bilateral



papilloedema of 2 to 3 diopters. The right pupil was slightly larger than the left but both reacted normally. The visual fields were full on repeated examination. There were no other abnormal findings. A ventriculogram was attempted. The needle inserted into the left occipital lobe encountered a cystic cavity at a depth of 2 cm. from which syrupy yellow fluid was obtained.

Electro-encephalography showed absence of alpha waves on both sides even when the amplification was increased to several times that normally employed. Slow negative swings were seen chiefly in the left occipital lead. These were irregular but at times came about twice in 5 secs. Such a succession of swings is seen in Fig. 13 where they appear from the left occipital lead in contrast to the right occipital which shows nothing. It is probable that they represent localized pressure in this area. No definite waves in the neighborhood of 1 or 2 per sec. were seen.

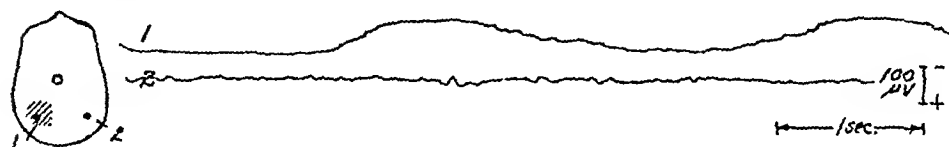


FIG. 13. Case 9. Slow swings localized to area of tumor.

At operation a large glioma (atypical astrocytoma) was found occupying most of the left occipital lobe. The entire lobe including the tumor and the cystic cavity was amputated. She made an excellent recovery except for a persistent right homonymous hemianopia.

CASE 10. (G. Z., No. 125436), a white male, 34 years of age was referred by Dr. A. H. Barnett of Chicago. He was admitted on December 3, 1937. Three years previously he had suffered his first attack. It began with a "numb" feeling in the epigastrium, an inability to speak, then loss of consciousness and a generalized convulsion. At first these attacks occurred at intervals of three to four months but just prior to admission had grown more frequent. From the first there was an associated slight weakness of the right arm and frequent twitchings of the right leg when in bed at night. During 1937 he had several attacks in which he would not lose consciousness but the right arm and leg would "draw up" and he would lose the power of speech. Examination revealed no abnormality except that rapid alternating movements were performed poorly by the right upper extremity.

Electro-encephalography showed delta waves, usually rather irregular, but sometimes sharp and clear at a frequency of about 2 per sec. These were quite sharply confined to the left frontal area. Fig. 14 shows tracings from the left frontal, right frontal and right temporal areas. Two per sec; waves are seen in the tracing from the left frontal area only.

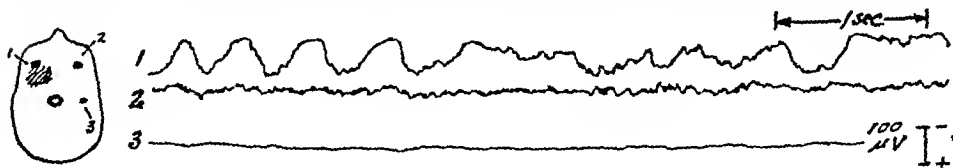


FIG. 14. Case 10. At 1, delta waves over tumor.

Ventriculography showed displacement of the anterior ventricular system downward and to the right. At operation a large glioma (astrocytoma) was found occupying the central portion of the left frontal lobe, extending backward almost to the precentral sulcus. The antero-superior one-third of the left frontal lobe was amputated and the tumor extensively removed. He has had no further attacks and has made an excellent recovery.

CASE 11. (M. L., No. 115439), a white female, 34 years of age, was first admitted on May 19, 1935 complaining of left-sided convulsive seizures and weakness of the left side of the body. For 7 years she had suffered from three or four convulsive attacks a year. The convulsive movements involved only the left side of the mouth, the left arm and leg. In some of the attacks consciousness was lost. In September, 1933, she began to develop weakness of the left arm and in July, 1934, the left leg became similarly affected. This weakness grew progressively more severe. In July, 1933, a pneumo-encephalogram was performed

elsewhere which was said not to indicate the presence of a tumor. Examination revealed little or no facial weakness but a marked weakness with severe spasticity in the left upper and lower extremities. The tendon reflexes were all hyperactive on the left side and Babinski's sign was present. The abdominal reflexes were absent on the left side. Reflex forced grasping was present in the left hand. Sense of position was impaired in the fingers and toes on the left side.

At operation on May 25, 1935, a large glioma (astrocytoma) presented on the surface of the postero superior portion of the left frontal lobe. It measured 6 X 5 cm. on the surface. It extended posteriorly to the anterior margin of the pre central gyrus and inferiorly to the inferior margin of the second frontal convolution. An extensive block dissection was made.

Following this operation she continued to have a severe left hemiplegia. Convulsions were readily controlled with phenobarbital but returned whenever the medication was omitted. In June, 1937, she began to suffer from occasional attacks of severe headache, nausea and vomiting. On November 10, 1937, the decompression began to bulge markedly and she was readmitted on November 12, 1937. Examination revealed nothing additional.

At that time electro encephalography was done. It revealed slow negative swings in both frontal leads equally. These occurred roughly about once in five seconds, were not seen in the other leads. Large alpha waves were present in both occipital leads and were also obtained, although in a more broken fashion and not so continuously, from the whole cranial surface. They appeared to be somewhat increased in amplitude. Over the region of the tumor occasional small runs of delta waves having a frequency of 1.3 per sec. were seen. They were of small amplitude and somewhat obscured by the concomitant faster disturbances which were largely of alpha frequency. Fig. 15 shows an electro encephalographic tracing using two channels, one from each temporal region. The one on the right temporal region shows small 1.3 per sec. waves in contrast to the one from the opposite side which shows none. Marks have been placed below the record to emphasize the delta waves.

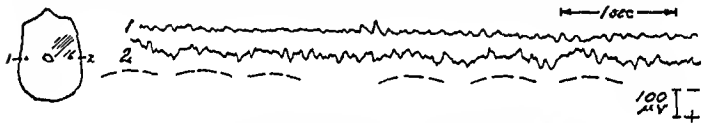


FIG. 15 Case 11. At 2, small delta waves from region of large tumor.

This patient died suddenly on the following day. Autopsy revealed on the right side a very extensive, deeply seated infiltrating glioma extending from the central sulcus about two thirds of the distance to the tip of the frontal lobe, crossing in the corpus callosum and involving the left frontal lobe to some extent. This case is presented as an example of a large tumor with minimal findings. It is possible that the subtemporal decompression may have lowered the local pressure and reduced the electrical disturbances.

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# THE EFFECTS OF ABLATION OF THE CORTICAL MOTOR FACE AREA IN MONKEYS\*

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## I. INTRODUCTION

THE PHYSIOLOGICAL significance of the cerebral cortex is not completely revealed by its responses to electrical stimulation, but the results of surgical ablation of these areas, when correlated with results of electrical stimulation give more complete insight into its function. In this paper the effects of surgical removal of the "motor face areas" will be presented and the results correlated with the electrical excitability of these regions (Walker and Green, 1938). The results offer a more complete physiological basis for localization of cerebral lesions.

## II. HISTORICAL NOTE

Bouillaud introduced in 1830 the experimental approach to cerebral localization. His investigations of the effects of local cortical ablations in dogs on vocalization pointed to a localization of function within the cerebral cortex. Clinical observations (Broca, 1861-63), have been largely concerned with the speech defects from cortical destruction (Delavan, 1885), the less striking somatic phenomena being relegated to the background. With the advent of neurological surgery (Nancrede, 1888, and Lloyd and Deaver, 1888) observations on the effect of local ablations and extensive cortical resections (Dandy, 1933; Gardner, 1933) involving the face motor area have multiplied rapidly; experimental studies, however, have not been extensive.

Grünbaum and Sherrington (1903) described a crossed hemiparesis involving the lower facial musculature following ablation of the face area of a chimpanzee. In 1917, Leyton [Grünbaum] and Sherrington removed from a chimpanzee the cortex of the left precentral gyrus which upon electrical stimulation caused closure of the eyelids, but could detect no abnormality in the appearance of the animal. Even after removal of the comparable area of the right hemisphere, the eyelids were readily closed, although much less vigorously. Subsequent cortical stimulation did not produce movement of the eyelids. In another chimpanzee removal of the entire left precentral cortex, with the exception of a strip 1-2 mm. wide along the central sulcus, caused a right sided flaccid paralysis with bagging of the cheek. The nasal fold was less marked and the lips remained slightly open on the right side. "The tongue lay with its midline, especially just behind the tip, slightly to the left of the midline of the mouth," but no difference could be detected in the posture or movement of the forehead, eyebrows or upper eyelids. In a third chimpanzee ablation of the inferior part of the precentral convolution anterior to the electrically excitable cortex which yields movements of the face (corresponding to areas 6b $\alpha$  and 6b $\beta$ ) caused no paralysis or other disturbance except "possibly slightly increased excitability." There was no change in vocalization.

Decorticate dogs have been studied by Goltz (1892), Zeliony (1913), and Rothmann (1910, 1923), decorticate cats by Dusser de Barenne (1919), Bard and Rioch (1937), and Hambourger (1937), and decorticate monkeys by Karplus and Kreidl (1914). Bard and

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Rioch conclude "it is clear that the basal olfactory areas together with the associated ventral portion of the striatum and lower centers with which they are connected, namely, the hypothalamus, subthalamus and reticular substance of the brain stem, are capable of elaborate feeding reactions of a highly complicated type"

### III. METHODS

For adequate study of the functions of the various areas and determination of the factors responsible for recovery, several types of experimental procedure were employed unilateral and bilateral extirpations of areas 4 and 6 (face region), simultaneously or successively, and section of the peripheral hypoglossal nerve. The term, area 4c, will be used to refer to the face portion of area 4 only and area 6 (face) will be taken to include areas 6b $\alpha$ , 6b $\beta$  and the lower portion of area 6a $\alpha$ . The landmarks of these areas have already been described (Walker and Green, 1938). In all animals the extent of the lesion has been verified by complete serial section of the lesion and also of a generous amount of adjacent cortex. The ablated tissue was studied microscopically, in some cases in serial sections. In many instances the cortex was stimulated just prior to sacrifice to determine physiologically the completeness of the lesions. The type of operative procedure, duration of the period of observation and other pertinent data concerning the animals used in this investigation are included in Table I in which areas 4 and 6 refer to the face portion of these areas, i.e., to areas 4c and 6a and b (lower part).

### IV. RESULTS

#### 1. Unilateral ablation of the entire face areas 4 and 6

*Areas 4c and 6.*—Following complete unilateral ablation of the motor and premotor face areas the muscles of the lips are completely paralyzed, the palpebral fissure is wider and closure of the eyelid weaker on the contralateral side. The buccal pouch on the paralyzed side becomes distended, and food, lodging between the teeth and cheek, falls from the buccal cavity. The body of the tongue lies in the midline, or slightly to the paralyzed side, with the distal third curled to the side of the lesion and the extreme tip at times curled underneath and towards the opposite side. Stimulation of the floor of the mouth on the paralyzed side causes vigorous rotation of the tongue to that side, but stimulation of the other side elicits little or no response. The ipsilateral half of the tongue seems to contribute to the movements to a far greater extent than the contralateral half. When the tongue is protruded it assumes an exaggeration of the resting position. A month after operation the palpebral fissures are equal and a considerable degree of facial movement has become apparent. After about three weeks the tongue can be rotated to the side of the lesion, but never as fully as to the contralateral side.

*Experiment 1. Initial ablation of left face areas 4 and 6.* Severe transient paresis of contralateral facial muscles and tongue. *Macaca mulatta*, A 6 62. Weight, 2700 gms.

*First operation, January 5, 1936.* Under sodium amytal anesthesia a left osteoplastic flap was reflected, the pia incised with the Bovie unit, and the cortex of areas 4 and 6 (face area) ablated by a subpial dissection.

*Postoperative notes—2nd day.* The animal was in good condition. The right palpebral fissure was slightly larger than the left, and there was a marked weakness of the right lower facial muscles. The body of the tongue lay in the midline but the tip curled to the left. Stimulation of the floor of the mouth on the right side resulted in vigorous rotation of the tongue to the right, whereas similar stimulation of the left side caused practically no movement. Vocalization was poor, but swallowing normal.

*5th day.* The reaction to pin prick on the right cheek and shoulder seemed slightly diminished. The masseters contracted equally well on the two sides. The jaw jerk was not

TABLE I

No.	Animal*	Operations	Inter operation interval	Total post-operative observation period	Terminal stimulation	Comment
33	M	Initial ablation: left areas 4 and 6; secondary ablation: right areas 4 and 6	5 mos.	11.5 mos.	Yes	
62†	M	As above; tertiary ablation, left inferior postcentral gyrus	1 mo. $\frac{1}{2}$ mo.	8 wk.	Yes	Respiratory tracings made pre- and post-operatively
34	M	Ablation left areas 4 and 6		8 wk.		Died immediately following removal right areas 4 and 6
55	M	Same		16 days		Marchi degeneration
35	M	Ablation right area 6		4.5 mos.		Left cortex exposed previously; stimulation unsatisfactory
46	M	Ablation left area 6		14 days		Marchi degeneration
56	M	Ablation left area 4		14 days		Marchi degeneration
S.P. 16	B	Ablation left area 4		5 mos.	Yes	
S.P. 19	B	Ablation left area 4		2 mos.		
61†	M	Initial ablation: left and right areas 4; secondary ablation, left area 6	2 wks.	2 mos. + +	Yes	
32	M	Ablation left and right areas 4 and 6		8 days		Sacrificed on 8th postoperative day scalp infection
65†	M	Ablation left areas 4 and 6; section left hypoglossal nerve		4 wks.	Yes	
63†	M	Initial ablation, left area 6; secondary ablation, right area 6	2 wks.	6 wks. +	Yes	Respiratory tracings made pre- and post-operatively
70	M	Section left hypoglossal nerve		5 days		
71	M	Initial left hemidecortication; secondary right hemidecortication	6 wks.	7 wks.		
72	B	Same	2 mos.	2 mos.		

\* M—monkey; B—baboon.

† Brief abstracts of the protocols of animals Nos. 62, 63, 61 and 65 are included in this paper as Experiments 1, 2, 3 and 4 respectively.

At the beginning of this investigation reliance was placed mainly on observation of the behavior of the animal in the cage—its cry, emotional expression and mastication. It soon became evident that these activities depended upon primitive mechanisms which cortical lesions affected only slightly. Further procedures therefore were introduced, touching with a blunt probe the outside of the cheek, the buccal mucous membrane, the tongue and the soft palate, comparing the complexity of the responses, on the paralyzed side with those of the normal side, or with those of the normal animal. These tests made possible the detection of abnormalities in the motor performance of the facial and lingual musculature which would otherwise have gone unnoticed. Observation of the animal's attempt to remove the irritating probe from the mouth or prevent its entrance was found to be particularly informative.

exaggerated. The left cheek moved vigorously when touched but the right was immobile when similarly stimulated. Food remained in the right side of the mouth between the cheek and teeth but the food pouches were about equally filled.

*6th day* The right palpebral fissure continued larger than the left and the right lower facial weakness was prominent. Part of the time the tongue lay in the midline and at other times slightly to the right of the midline; the tip curled always to the left and usually lay to left of the midline. Rotation of the tongue as described above was again noted. The left side of the tongue seemed to participate in this movement much more than the right. The temperature response to cooling and warming was the same on the two cheeks.

*12th day* There was a slight movement of the right side of the face but much weaker than the left. The weakness was much more apparent on volitional than on emotional grimacing. The tongue was rotated and deviated to the right much better than to the left. No dysphagia was present and vocalization was good.

*21st day* Only a slight facial weakness was present. The body of the tongue was in the midline with the distal third to the right of the midline; the extreme tip curled underneath and to the right. The tongue could be rotated and deviated to either side, but both movements were through a fuller range to the right.

*27th day* The palpebral fissures were equal. The right side of the mouth moved fairly well both voluntarily and emotionally but movements were less marked than on the left. The tongue could be protruded but usually the distal third was slightly to the left with the extreme tip curled to the right. The animal vocalized well. On the 28th day following the first operation the "motor face" cortex was removed from the right hemisphere. The subsequent findings are presented in Section 2 p 266 (see also Experiment 4, Section 5, p 273).

*Unilateral extirpation of area 4c* Removal of area 4c resulted in a marked paresis of the opposite lower facial musculature lasting from 8 days to over 5 weeks, and slight widening of the contralateral palpebral fissure. The longer paresis would appear to be more characteristic since the rapid recovery occurred in an animal in which a fringe of electrically excitable area 4c cortex remained. The range of lingual movement was markedly diminished, particularly when the animal attempted to execute complicated motions with the tongue. In its resting position the body of the tongue lay approximately in the midline. Rotation of the tongue to the ipsilateral side was impaired. Later (5-6 weeks) this function was partially recovered.

*Unilateral extirpation of face area 6* Ablation of the lower part of areas 6a $\alpha$ , 6b $\alpha$  and 6b $\beta$  produced a transient paresis of the contralateral lower facial musculature but no inequality of the palpebral fissures. The tongue usually lay in the midline and in response to stroking the floor of the mouth deviated and rotated only to the side opposite the lesion. In contrast with the sequelae of area 4 lesions these signs disappeared rapidly. By one week the tongue could be moved equally well to either side and the paresis of the lip was almost gone.

*Experiment 2 Ablation of left area 6 (face), transient contralateral facial weakness and lingual paresis* Macaca mulatta A 6 63 Weight 2800 gms

*First operation* June 15, 1936 Under sodium amytal anesthesia a left osteoplastic craniotomy was performed. Using subpial dissection area 6 (face) was ablated.

*Postoperation notes—2nd day* The right corner of the mouth drooped slightly but could be retracted. The masseters contracted strongly, the tongue lay slightly to the left of the midline, and could be rotated and deviated fully to the right but poorly to the left.

*5th day* The masseters contracted equally on both sides. The slight right lower facial weakness was still evident. The tongue lay in the midline and could be rotated and deviated equally well to either side. The voice was normal.

12th day. There was a slight lag in retracting the right angle of the mouth, but otherwise no abnormalities were apparent in the cranial nerves. On the thirteenth postoperative day, the right face area 6 was removed (see p. 270).

## 2. Bilateral ablation of the motor and premotor areas

Practically complete loss of motion of the lower facial muscles and of the distal half of the tongue occurred initially. The pouches remained filled; food clung between the teeth and the cheeks and spilled from the buccal cavity. The voice was a feeble chirp or low pitched and husky; the characteristic noisy chatter and variation of intonation were absent. The bite was often weak or more often was normal. Slight movement of the angles of the mouth and rotation of the tongue could be elicited within about three weeks, by which time also the distention of the pouches had become less prominent, but complete recovery of movement did not occur. Stimulation of the posterior wall of the pharynx elicited a contraction of the posterior half of the tongue rarely sufficient to protrude the tip past the lower teeth. Only weak contractions of the intrinsic muscles of the distal third of the tongue could be seen.

*Experiment 1 (continued). Secondary ablation of right face areas 4 and 6; severe bilateral facial and lingual paresis with slow recovery. Tertiary ablation of inferior portion of left post-central cortex; practically no change in motor status (continued from p. 265).*

*Second operation. February 2, 1936.* Twenty-eight days after ablation of the left face areas 4 and 6 the animal was anesthetized with sodium amytal and a right osteoplastic flap reflected. The central, inferior precentral and sylvian sulci were opened and the cortex lying between them removed in one piece. The lesion extended superiorly to the vein marking the upper border of the face area.

*Postoperative notes.* Neither hand was used well and food fell often from the hands during feeding. The mouth was opened and closed readily. The response to pin prick was equal on the two sides of the face. The right cheek retracted slightly when the right side of the buccal mucous membrane was irritated, but no response occurred on the left side to such stimuli. The tongue lay flat in the mouth; only its posterior half moved. Food hung from the lips and corners of the mouth. No jaw jerk could be elicited. The voice was low pitched and feeble.

29th day. The right palpebral fissure was larger than the left. Both eyes could be closed strongly. The only lingual movement was elevation of the posterior half of the tongue.

30th day. The grimacing characteristic of the macaque monkey was not seen and the lower facial muscles were immobile, except for a slight retraction of the right cheek when the buccal mucous membrane was irritated. The masseters contracted forcibly on both sides. The animal made no attempt to swallow when food or water was placed in its mouth. Accordingly 200 cc. of milk were given by stomach tube. The palpebral fissures were equal.

32nd day. The movements of the right side of the face were increased in range and strength. The voice was stronger but still low pitched and lacked the usual range of intonation. The palpebral fissures were equal and the eyelids closed vigorously.

37th day. The right cheek could be retracted slightly but retraction of the left cheek was still absent. The tongue lay in the midline; the only movement observed was elevation of its body.

40th day. The left food pouch was full, the right empty. The tongue was protruded over the teeth, but was not rotated.

*Third operation. February 17, 1936.* On the 15th day following the second operation the animal was anesthetized with sodium amytal, the left bone flap reelevated, and the inferior portion of the postcentral convolution ablated.

47th day. The left food pouch which had been consistently dilated was now about the same size as the right. There was perhaps slightly increased tone in the right food pouch, when tested with the examining probe. The right corner of the mouth could be retracted but the left remained immobile. There was about 10° rotation of the tongue to the left with slight curvature of the body to the right.

*49th day* Both angles of the mouth could be retracted about 2-3 mm upward and backward. The animal still had difficulty keeping food in its mouth. The cry remained weak. There were gross movements only in the posterior and middle thirds of the tongue with only slight changes in contour of the distal third. The tongue could be rotated about 20-30° to either side and protruded about 2 mm over the teeth.

*57th day* The findings were approximately the same as previously. Only the posterior one third of the tongue could be rotated. Slight narrowing of the distal third of the tongue occurred during elicitation of the gag reflex.

*Terminal stimulation* March 2 1936 On the 13th day after the third operation the animal was anesthetized with ether and the operative sites on the cortex of each hemisphere



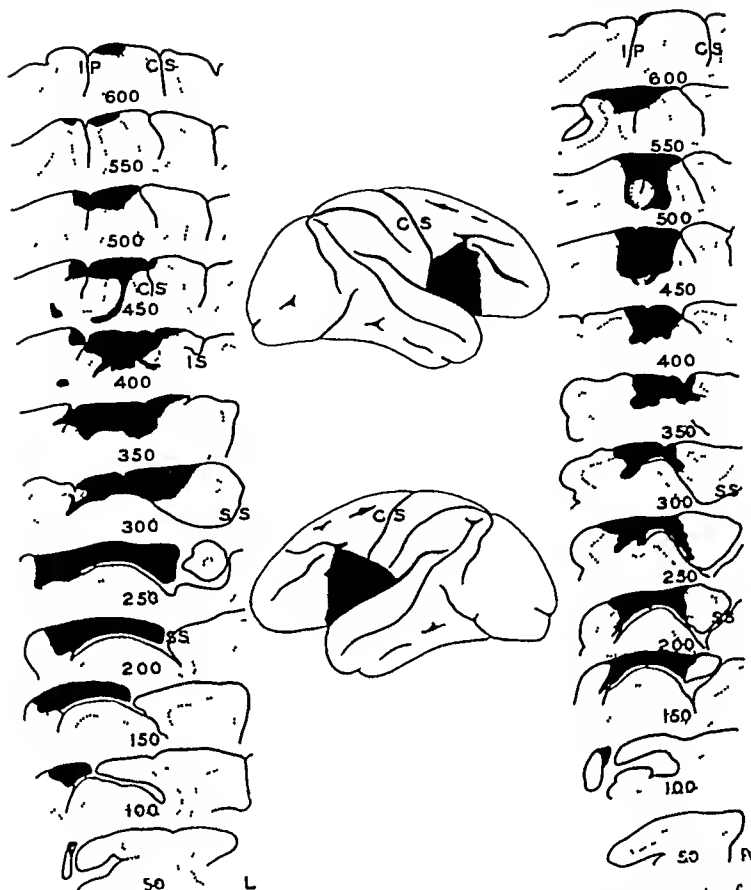
Fig 1 Photomicrograph of a serial section through the cortex of the right face area in Experiment 1, including the central sulcus and the tissue remaining immediately anterior to this sulcus. The section is taken through a point in the cortex, marked with India ink, which yielded retraction of the left angle of the mouth and slow deviation of the tongue to the left at the terminal stimulation experiment.

reexposed. No responses could be obtained upon stimulation of the cortical face area on the left side, but on the right, from a point on the central sulcus, retraction of the left angle of the mouth and slow deviation of the tongue to the left were produced (see Fig 1). Another point below the inferior precentral sulcus gave rise to rhythmical movements of the tongue and jaw.

*Postmortem examination* Body weight 2400 gms, brain weight 65 gms. Gross examination of the body showed no abnormalities. In the right hemisphere the ablation damaged the inferior portion of area 3. The anterior inferior part of the ablation was bounded by granular frontal cortex except for the most inferior sections in which agranular frontal cortex was present on the anterior margin of the lesion. Hence practically all of areas 4c and 6 (face) had been removed. In the left hemisphere the lesion extended superiorly along the posterior lip of the inferior limb of the precentral sulcus, damaging only superficially the granular cortex anterior to the latter sulcus. It extended posteriorly to the central sulcus, crossed it and passed just below the inferior tip of the intraparietal sulcus. The posterior margin of the ablation was bounded by area 2 cortex, area 7 and the cortex of the island of Reil appeared not to have been damaged (Fig 2).

*Bilateral ablation of area 4* Immediately following a bilateral extirpation of area 4 the range of movement of the muscles of the lower half of the face was markedly diminished, although sucking movements could be obtained by





stroking the dorsum of the tongue. Vigorous stimulation of the posterior wall of the pharynx elicited slight humping of the posterior part with forward and backward movement but no evidence of active contraction in the anterior two thirds of the tongue. After approximately  $1\frac{1}{2}$  months slight rotation of the tongue to either side could be obtained and this movement increased in range until about  $60^\circ$  rotation was present, but it was never possible to obtain significant deviation of the tongue. Although, after two months, slight contractions could be observed in the distal half, resulting in narrowing of the tip, the tongue was poorly protruded.

*Experiment 3. Simultaneous bilateral ablation of area 4c, severe bilateral facial and lingual paresis. Secondary ablation of left area 6 (face), slight increase in right facial and lingual paresis. Macaca mulatta A 6-61. Weight 2700 gms*

*First operation May 29, 1936* Under nembutal anesthesia, a bilateral osteoplastic craniotomy was performed. The pia was incised with the Bovie unit and area 4c on each side ablated.

*Postoperative notes—1st day* The animal was in good condition. Both corners of the mouth retracted feebly when the animal attempted to bite. Eye movements were normal. The bite was vigorous, the cry high pitched. The tongue could be moved forward and backward, but lateral deviation was not observed.

*6th day* There appeared to be some excessive salivation, perhaps due to inability to prevent the saliva from drooling from the corner of the mouth. The reactions of the orbital and ocular muscles were normal.

*9th day* Food was constantly present between the teeth and cheeks, and the mouth appeared more unkempt than normal for a monkey.

*13th day* The weakness of cheek muscles was still prominent but the range of retraction of the lips was increasing. The tongue lay in the midline and was moved forward, backward and sideways slightly. Its posterior half could be elevated. Most of the movements were made with the body of the tongue, the tip remaining immobile. The jaw jerk was not exaggerated.

*28th day* The tongue moved forward and backward as a unit while the tip remained stationary, thus forward movements resulted in doubling the tongue over itself. The tip was not moved out over the lower teeth and no rotation was present.

*44th day* Facial and labial, and biting and crying movements were feeble. The tongue could be rotated 20–30° to each side. A swallowing reflex could be elicited by stroking the posterior wall of the pharynx but the associated tongue movement was limited to its posterior part.

*56th day* Both sides of the mouth retracted slightly, the left better than the right when the animal was excited or cried, but the reverse was true when the movement was voluntary. Sucking movements were made with the lips and tongue when the tongue was stroked. The food pouches were empty. Contraction of the intrinsic muscles of the distal third of the tongue with slight narrowing was observed for the first time. The tongue could be rotated about 60° to the left and 45° to the right. The tongue was extended in the midline 2–3 mm over the lower teeth.

*Second operation July 24, 1936* On the sixtieth day after the first operation the animal was anesthetized with ether and the left face area reexposed. Stimulation of remaining cortex yielded only slight retraction of the right angle of the mouth from a point high along the central sulcus in the face area and rhythmical movements of the tongue from along the inferior precentral sulcus. The cortex lying anterior to the previous ablation, inferior to the precentral sulcus, and extending to the sylvian sulcus was ablated by blunt dissection, the dura replaced but not sutured, and the bone flap replaced.

*57th day* When the animal cried, the left side of the face was retracted sufficiently to expose the molars, the right side enough to expose the incisors. Stroking the cheeks resulted in better pursing movements on the left. The left palpebral fissure was slightly larger than the right. Stroking the tongue resulted in pursing of both lips, narrowing of the distal third of the tongue and elevation of the jaw. The tongue could not be deviated nor protruded to the teeth, but could be rotated about 30° to the right and only about 10° to the left, and could not be deviated. There was increased resistance to opening the jaw.

*58th day* The palpebral fissures were equal. The lips moved to a greater extent on the left than on the right in response to both excitement and stroking the cheek. The tongue rotated about 15° to the left but none to the right.

*61st day* The tongue rotated to the right about 20° and to the left 5°. No movements could be elicited in the tip of the tongue.

*65th day* Both cheeks could be retracted about 2–3 mm. The posterior half of the tongue rotated about 20° to either side upon stimulation of the floor of the mouth. When the gag reflex was elicited the tongue was pushed forward to the teeth. No deviation of the tongue but slight narrowing of the distal tip was observed.

*Terminal stimulation* On the 9th day following the second operation the animal was sacrificed under deep anesthesia. Because of extensive adhesions it was deemed unwise to attempt to remove the dura over the left cerebral cortex. The cortex on the right side was exposed and stimulated with 60 cycle alternating current. Complex rhythmical jaw and tongue movements were obtained from the remaining cortex of area 6. Stimulation of the anterior margin of the central sulcus in the upper part of the face area produced retract

tion of the left angle of the mouth and deviation of the tongue to the left. Points a short distance from this anteriorly and posteriorly gave the same response, but with a longer latency (spread?).

*Postmortem examination.* Body weight 2700 gms.; brain weight 75 gms. Gross examination of the body showed no abnormalities. In the right hemisphere the lesions involved all of area 4c, except a strip along the anterior margin of the central fissure. It damaged the adjacent areas 6a $\alpha$ , 6b $\beta$  and 3 but did not involve the frontal granular cortex or the postcentral convolution. In the left hemisphere the lesion almost completely removed areas 4c and 6a $\alpha$ , 6b $\alpha$  and 6b $\beta$  from the inferior part of the precentral convolution and damaged the cortex of the frontal granular region. Two softenings, one in the postcentral convolution and a second in the temporal region, complicated the ablation (Fig. 3).

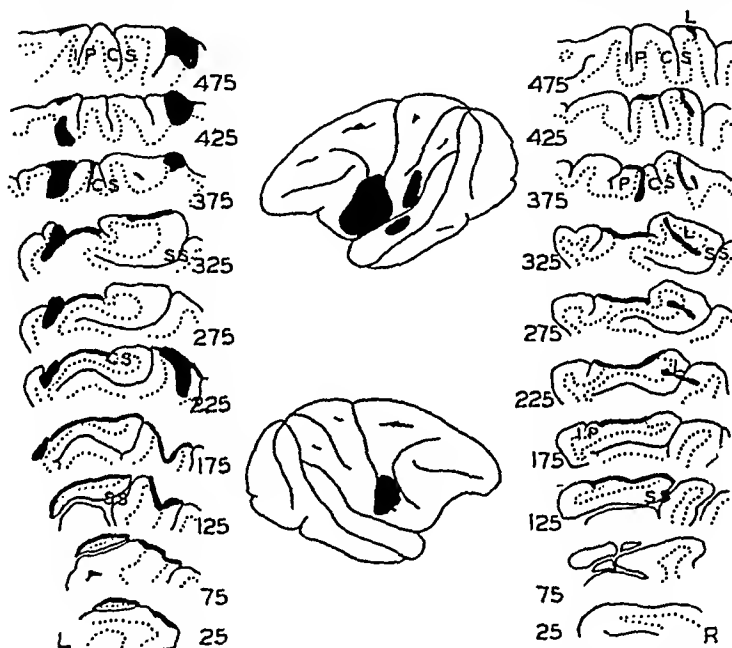


FIG. 3. Drawings showing the external configuration and the extent of the cortical ablation in Experiment 3. See Fig. 2 for legends. L, incision made in right cortex toward the end of the terminal experiment.

*Bilateral ablation of area 6.* Initially there was paresis of the lips and reduction of the range of lingual movement. Within one week the movement of the cheek and lingual muscles greatly increased and contractions were observed in the intrinsic tongue muscles. By the end of four weeks it was difficult to detect any signs of paralysis.

*Experiment 2 continued. Secondary ablation of right area 6 (face); transient bilateral facial and lingual paresis.* (Continued from p. 266.)

*Second operation. June 28, 1936.* On the 13th day after ablation of the left area 6 (face) a right osteoplastic craniotomy was performed under sodium amytal anesthesia and area 6 (face) removed by subpial dissection.

*14th day.* There was a slight bilateral facial weakness. The tongue lay in the midline but was not rotated well to either side.

*17th day.* The masseters contracted well. The jaw jerk was not exaggerated. The left side of the face lagged slightly behind the right when the corners of the mouth were retracted. Vocalization and swallowing were normal.

*21st day* No facial weakness could be detected. The tongue could be protruded well past the teeth, rotation was limited to  $45^{\circ}$  to either side and deviation was slightly impaired to both sides. The intrinsic muscles of the tongue contracted vigorously.

*37th day* There was no facial or lingual weakness. The animal appeared normal.

*Terminal stimulation experiment* On the 32nd day after the second operation the animal was anesthetized with ether and the cortex stimulated. Typical sustained responses were obtained from the remaining cortex of area 4 on both sides. On the left side rhythmical movements of the tongue and jaws were elicited from the posterior margin of the ablation (see Fig. 4).

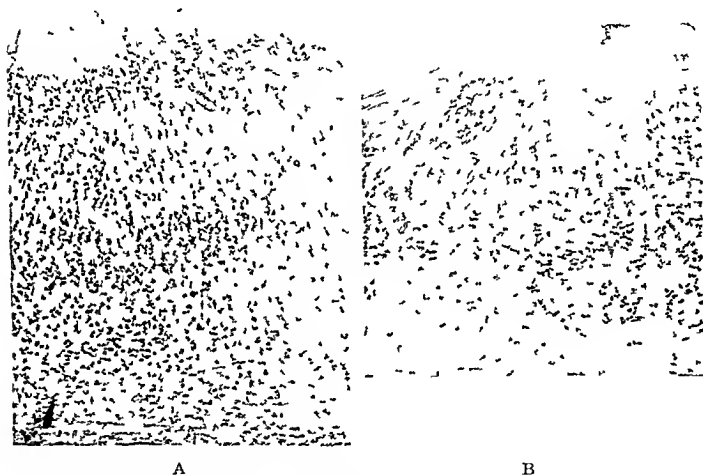


FIG. 4. Photomicrographs of two serial sections of the cortex in Experiment 2. In this experiment an attempt was made to remove area 6 (face) bilaterally. On terminal stimulation rhythmic movements of the tongue were obtained from excitation near the left anterior subcentral sulcus. Here transitional cortex (6ba and 3b) with large cells in the lower portion of the third and upper parts of the fifth layer were found (Section A). On the opposite side no such response could be obtained and histologically there was no semblance of area 6ba tissue (Section B).

*Postmortem examination* Gross examination of the body showed no abnormalities. In the right hemisphere the lesion had almost entirely removed area 6, damaged a small part of the lower portion of area 3, and undermined a small portion of the granular frontal cortex. On the left side the lesion had entirely spared area 3, removed most of the lower part of area 6, and slightly damaged the frontal granular cortex (see Fig. 5).

### 3. Observations peculiar to serial ablations of the cortex

When the ablations of the motor face areas are carried out in sequence the paralysis resulting from removal of the second area is more than double that resulting from unilateral extirpation. There is considerable recovery in

the retraction of the angle of the mouth opposite the initial lesion after about two months. Immediately after the second operation the movements of this cheek are greatly impaired, but recover more rapidly than those of the newly paralyzed cheek. About two months after the initial lesion, the tongue can be rotated normally to the contralateral side and has recovered about 45-60° motion towards the side of the lesion; but immediately after the second operation this recovered movement to the ipsilateral side is markedly decreased and never completely recovered (see Experiment 1, Section 1a, p. 263; and Section 2, p. 266).

While removal of area 4c subsequent to a bilateral extirpation of area 6 (face) would be of interest its particular significance was not considered im-

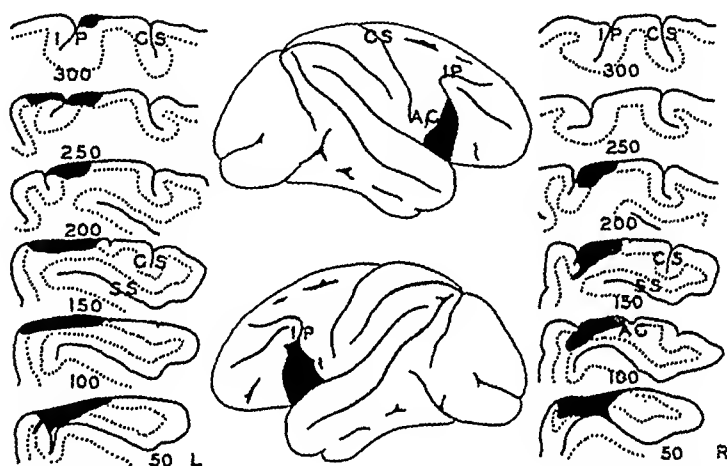


FIG. 5. Drawings showing the external configuration and extent of the cortical ablation in Experiment 2. See Fig. 2 for legends.

portant, because of the normally greater degree of paralysis following the former operation compared with the latter. However, the effect of removal of an area 6 (face) subsequent to a bilateral removal of area 4c should give a clue to the function of area 6 (face), particularly the part the latter might play in recovery. In one animal (Experiment 3, Section 2, p. 268) that recovered motility in the lips contralateral to the second ablation was considerably decreased, rotation of the tongue was diminished, and the activity of the intrinsic muscles of the distal third was impaired. This difficulty was not as permanent as that seen in complete bilateral ablations of the motor face areas perhaps explicable by ipsilateral innervation from the remaining area 6 (face).

#### 4. Generalizations common to all lesions

A number of findings, mainly negative, were common to most lesions. In many animals the bite was weak for the first few hours postoperatively but after the second day no reduction in strength could be detected. No defi-

nite deviation of the jaw was noted and the two masseters always contracted equally. Dysphagia was never apparent. A definite jaw jerk was present only in one monkey which had had a complete bilateral decortication. In a few animals slight paresis of the arms was seen, probably due to coincidental damage to the suprajacent arm area. Although movements of the ears cannot be judged accurately because of the operative procedures no loss of motion was apparent. Transient diminution of sensation about the face appeared to be present in one animal.

### 5. *Ipsilateral representation*

In our previous paper it was demonstrated that movements of the tongue can still be produced by cortical stimulation of the contralateral face area after the hypoglossal nerve has been sectioned, and that in the normal animal rotation and deviation to either side can frequently be obtained by stimulation of a single area. These findings suggest that each half of the tongue is bilaterally represented in the cerebral cortex, or in other words, that there is ipsilateral cortical representation of the lingual muscles. In order to test this assumption further in a chronic experiment, the entire face area was removed from one hemisphere and the hypoglossal nerve sectioned on the same side. In this preparation lingual movements had to originate either subcortically or in the ipsilateral hemisphere.

*Experiment 4 Simultaneous ablation of the entire left face area and section of the left hypoglossal nerve, right facial paresis and severe impairment of lingual movement Macaca mulatta A 6 65 Weight 2400 gms*

*First operation July 8, 1936* Under sodium amytal anesthesia a left osteoplastic flap was reflected. The pia was incised with the Bovie unit and areas 4c and 6 of the face region were extirpated. Especial care was exercised to remove all area 4 tissue from along the central sulcus. At the same time the left hypoglossal nerve was sectioned below the ramus of the jaw.

*Postoperative notes—3rd day* The right side of the cheek was completely immobile except for slight retraction in emotional crying. The palpebral fissures were equal but a little more firmly closed on the left. The masseters contracted equally and strongly. The tongue lay motionless in the floor of the mouth. When the swallowing reflex was elicited the tongue elevated only posteriorly and slightly in its middle third. Considerable food was present in the buccal cavity—perhaps an indication of dysphagia.

*6th day* There was no real change in the status of the facial and lingual musculature.

*18th day* The palpebral fissures were equal. The right facial muscles moved feebly. The tongue at rest was slightly curved to the right side with the tip definitely to the right. The tongue could be rotated and deviated to the right fairly well but poorly to the left. There was no active movement of the left side of the tongue. It could be protruded past the teeth although usually somewhat to the right of the midline.

*21st day* There was poor volitional retraction of the right side of the mouth but it was strong under excitement, although less than on the left. At rest the tongue lay in the midline with the tip slightly curved to the right. When the tongue was stroked there was slight closing of the jaw and a pursing movement of the lips. The tongue could be rotated about 60° to the right and 20° to the left. Deviation of the tongue was observed to the right only.

*26th day* The right corner of the mouth could be retracted feebly, and closure of the lips on the right side was weak. Stroking the floor of the mouth produced deviation of the tongue so that the tip was placed over the right lower incisor, but no deviation could be obtained to the left. The body of the tongue could be rotated about 45° to either side and the distal third to the right about 60° but not more than 20° to the left. Stroking the pos-

terior wall of the pharynx produced a gag reflex, with the tongue protruded over the teeth and slightly to the left of the midline.

*Terminal stimulation experiment.* On the 26th day after the operation the animal was anesthetized with ether and the cerebral cortex bilaterally exposed. When the left cortex was stimulated, the only response in the face was obtained from a point on the central sulcus producing twitching of the right cheek and eyelids. Stimulation of the right cortex gave rise to strong responses in the oral and lingual musculature, both complex and discrete movements being observed.

*Postmortem examination.* Body weight, 2200 gms.; brain weight, 73 gms. Gross examination of the body showed no abnormalities. The cortex of the right hemisphere appeared quite normal except for a few ink marks made at the time of stimulation. The outline of the excitable area with a liminal stimulus, indicated with ink dots, corresponded closely with the cytoarchitectural outline of area 4, but the latter was slightly smaller than the

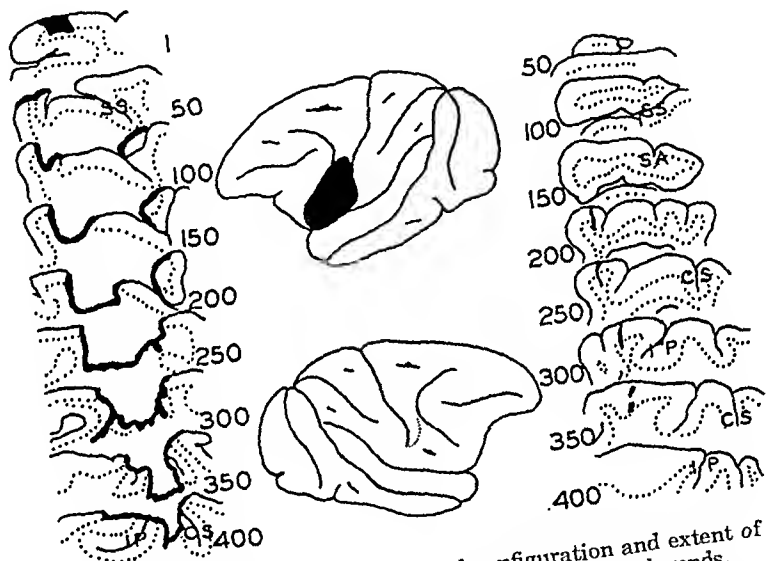


FIG. 6. Drawings showing the external configuration and extent of the cortical ablation in Experiment 4. See Fig. 2 for legends.

former, the difference being about 1 mm. throughout. The ablation of the left hemisphere had removed all the cortex of the motor and premotor region of the face area and damaged the adjacent cortex of the postcentral and frontal granular regions. There was no evidence of cortex of types 6a $\alpha$ , 6b $\beta$ , 6b $\alpha$  or 4c in the lower face area (see Fig. 6).

In order better to evaluate the above experiment, one hypoglossal nerve (left) was sectioned in another animal, the cortex being preserved intact. Following the operation the tongue lay about 2-3 mm. to the contralateral side. Deviation of the tongue to the contralateral side often associated with the angulation at the junction of the distal and middle thirds was possible, whereas the animal was quite unable to deviate the tongue to the ipsilateral side. Similarly rotation, evidenced by depression or elevation of the right half of the tongue, was possible to about 60° to the contralateral and only 5-10° to the ipsilateral side. The tongue could be protruded past the teeth usually to the contralateral side of the midline.

## V. DISCUSSION

Hughlings Jackson has emphasized that lesions of the cerebral cortex manifest themselves either by negative (paralyses) or positive (release) phenomena in either the somatic or autonomic spheres. Disorders of the former sphere, seriously impeding the activities of the individual, are more striking and impressive than those of the latter, and only recently have been reemphasized.

*Motor disturbances (paralyses).* Stimulation of the monkey's motor face cortex (Walker and Green, 1938) yields: (i) contractions of the lower facial musculature, limited almost solely to the contralateral side; (ii) contractions of both contra- and ipsilateral lingual musculature; (iii) occasionally and almost always bilaterally, movements of pharyngeal, laryngeal or upper facial muscles. It would be expected then that the negative phenomena resulting from unilateral ablation of these areas would not be a general paralysis but would show certain predilections; this indeed has been strikingly true. The most conspicuous weakness is that of the lower facial musculature; impairment is less pronounced in the tongue, and least of all in the pharyngeal, laryngeal and upper facial muscles. Recovery takes place in the reverse order, so that when little or no abnormality of the lingual musculature can be detected a lower facial weakness is still apparent. Evidence from the results of capsular lesions or cortical resections involving the face motor area (Grinker, 1934; Wechsler, 1935; Dandy, 1933; Gardner, 1933) indicates a similar relationship in the human being. If the motor face area be removed bilaterally the lingual as well as the lower facial movements are much impoverished, and those of the pharyngeal and laryngeal to a considerable extent impaired, while those of the upper facial muscles are but little depressed. From these observations during stimulations and after ablations one may conclude that, in the monkey, the lower facial and lingual musculatures are extensively, the pharyngeal and laryngeal considerably, and the upper facial musculature but little represented in the cerebral cortex.

A comparison of the results of stimulation both before and after section of the contralateral hypoglossal nerve, with those of unilateral, and bilateral removal of the motor face areas, and with those of ablation of one motor face area plus section of the ipsilateral hypoglossal nerve, leads one to the conclusion that in the monkey, although the lower facial musculature has largely a unilateral cortical representation, the lingual, laryngeal and pharyngeal muscles have extensive bilateral representation and that even the slight cortical representation of the upper facial musculature is largely bilateral. This last conclusion is in keeping with Leyton and Sherrington's (1917) observation in the chimpanzee.

The clinical manifestations of lingual involvement by a unilateral cortical, subcortical, or peripheral nerve lesion especially the deviation to the paralyzed side and poverty of movement, are all described in textbooks (Grinker, 1934; Wechsler, 1935; Jelliffe and White, 1935). Observations on experimental animals are necessarily incomplete. Monkeys with unilateral lesions



of the face areas 4, or 4 and 6 show the deviation of the tongue to the paralyzed side, and the poverty of movement characteristic of the clinical lesion. In addition, markedly impaired rotation of the tongue to the normal side was a characteristic feature of the unilateral preparations, although such a phenomenon does not appear to have been described clinically.

Although rhythmic movements are consistently obtained from electrical stimulation of 6b $\alpha$ , it is unlikely that their rhythmic nature is elaborated in the cortex since: (i) Magoun, Ranson and Fisher (1933) were able to obtain the similar rhythmic movements (lapping and mastication) from stimulation of the white matter of the internal capsule and basis pedunculi, and (ii) animals with bilateral ablation of the motor face areas and even complete decortications possess these movements sufficiently well to chew food and in some cases to eat unassisted.

*Autonomic disturbances.* In a previous paper (Walker and Green, 1938) respiratory changes and salivation were described as a result of stimulation of the premotor face area. Respiratory tracings have been made pre- and post-operatively from two animals, but no alterations were detectable. Following bilateral ablation of the motor face area drooling of saliva from the corners of the mouth is present for over a week. Whether this represents true sialorrhea, or is merely the result of inability to swallow is impossible to say in the absence of quantitative determinations of salivary flow. Skin temperature measurements of the face and extremities were recorded in one animal (Experiment 1, p. 265) after unilateral ablation of the face motor and premotor areas but no difference could be detected during or after change of the environmental temperature. The temperature of both sides of the face followed closely the rectal temperature.

*Release phenomena.* It is difficult to evaluate the rôle of "release" in the signs present following cortical ablations. Spasticity which is the outstanding phenomena in the extremities after lesions of the motor and premotor cortex, is difficult to determine in facial and lingual muscles. It is perhaps suggestive that the food pouches, moderately filled after eating in the normal animal, are, for a few days after a unilateral area 4, or 4 and 6 ablation, abnormally distended on the contralateral side, but are rarely filled to any extent upon recovery from the extirpation. In Experiment 1 (p. 266) approximately three weeks after the completion of a serial bilateral extirpation of areas 4 and 6, the pouch opposite the second operation had returned to about the same size as its fellow. When tested more resistance, however, was offered to the entrance of the examining probe on the side opposite the first operation. On the other hand, a similar test made on a hemidecorticate monkey six weeks after operation failed to show any difference in the resistance on the two sides. Increased resistance to opening the jaw has been noticed in three animals, one with bilateral ablation of area 4 (Experiment 3) and two with bilateral areas 4 and 6 lesions (No. 33, and Experiment 1), but in none of these was a definite jaw jerk elicited. The two completely decorticate animals showed both increased resistance to opening the jaw and the presence of a definite jaw jerk.

The forced laughter and crying which characterize bilateral supranuclear bulbar lesions in man, producing the pseudobulbar syndrome, have been lacking in our animals with double ablations of the cortical motor face areas. It is not improbable that such emotional disturbances are the result of lesions of the striatum or of the fibers from the latter rather than of the cerebral cortex. We have, however, noted frequently that an animal may respond, when excited, with a facial or lingual movement which apparently cannot be carried out volitionally. These responses are non-specific, violent, and poorly adjusted to the desired end, i.e., both sides of the mouth may be fully retracted by an animal, in which both face areas have been removed, if a painful stimulus is applied to a limb, or the animal is angered, although such movements are never seen in the normal behavior of the animal, nor can they be elicited by stroking the cheek or placing an object between the teeth. Similarly gentle stroking of the tongue or back of the throat in bilateral 4, or 4 and 6 preparations, fails to cause the normal protrusion of the dorsum of the tongue towards the irritating object, and it frequently fails to elicit any movement of the body of the tongue; but if the posterior pharyngeal wall is stimulated vigorously with the probe, producing a gag reflex, the entire length of the tongue may be protruded in the midline. These emotional or reflex movements occurring in an otherwise paralyzed organ, we believe, originate at subcortical levels. In support of this contention is the occurrence of essentially similar movements in completely decorticated animals. This dissociation of volitional and emotional facial responses is a fact well known clinically. It is even true that the paretic side may react before and to a greater extent than the normal side of the face.

*Regions responsible for recovery after cortical lesions.* Many investigators have discussed the factors responsible for "taking over control" following cortical ablations. The present study contributes the following evidence to the solution of this problem.

a. *Remaining homolateral tissue of the motor or premotor area.* It has been evident that the recovery was more rapid and complete in animals in which the removal of the motor and premotor areas was incomplete than in those in which the ablation included all of areas 4c and 6 (face). Animal No. 33 showed an unusual degree of recovery after a bilateral area 4c and 6 (face) ablation. At the time of sacrifice a considerable amount of electrically excitable cortical tissue was demonstrated, and histologically a part of 4c was spared. The responses to stimulation were essentially the same as those which the animal showed in the face and tongue in the clinical examination. In later experiments in which especial care was taken to make the lesions complete, recovery was slow, and stimulation of the cortex at the time of sacrifice rarely elicited a response. After bilateral ablation of area 4c, subsequent removal of area 6 intensifies the paralysis on the contralateral side.

b. *Ipsilateral representation in residual opposite motor or premotor area.* The evidence favoring ipsilateral cortical representation particularly that of the tongue, has been reviewed above (p. 273). Unquestionably this factor

plays a large part in the recovery of function after a unilateral ablation. Fulton and Dusser de Barenne (1933) have emphasized the importance of the ipsilateral representation of the tail, and Fulton and Keller (1932) and Bucy and Fulton (1933) that of the extremities. Foerster (1936) found in man that even skilled movements of the distal portions of the extremities might be regained after ablation of the contralateral motor cortex, but these movements were always associated with the same movement in the normal extremity. He concluded that they were due to ipsilateral innervation from the intact motor cortex. Evidence of ipsilateral representation of the extremities in the motor and premotor areas has also been furnished by the studies of Marchi degeneration in the spinal cord and of the degeneration of boutons of the spinal terminations of the cortical projections (Kennard, 1935; Hoff and Hoff, 1934; and E. C. Hoff, 1935). Ogden and Franz (1918) concluded that removal of the second motor area did not diminish the motility recovered as a result of forced usage in an extremity paralyzed by extirpation of one motor area.

c. *Sensory cortex.* It has been suggested that, since the postcentral convolution is a source of extrapyramidal fibers, it may play a part in the recovery of function after lesions of the motor areas. In one experiment following a bilateral motor and premotor ablation the postcentral sensory cortex was removed. No further impairment of cheek or lingual movement was observed after this procedure (Experiment 1).

d. *Subcortical centers.* Subcortical centers must play a considerable part in recovery of function since in Experiment 1 the terminal stimulation of the cortex failed to elicit most of the movements observed in the clinical examination, and the postmortem microscopical examination showed virtually complete ablation of the motor areas. More direct evidence is presented by the observations made on two animals following serial bilateral hemidecortications. About one month after the left hemidecortication and 3 days after the decortication of the right hemisphere slight retraction of the right cheek could be elicited by stroking the hairs of the face, and stroking the dorsum of the tongue caused slight rotation of the tongue towards the probe, more marked towards the left and associated with depression of the jaw and contraction of the cheek muscles. No movements could be elicited from the left cheek.

A large part of any recovery must be due to the subcortical structures. Certainly there is good reason to expect that the emotional responses may originate subcortically since Ranson (1937) has shown that they can be induced both in a normal and in a decorticated animal by stimulating the hypothalamus, and Bard (1928) has shown their spontaneous origin in decorticated animals, thus proving the presence of motor projection pathways from this region independently of the cortical projections. The preservation of the ability to close its eyes in the case of Leyton and Sherrington's (1917) chimpanzee, the considerable activity of the decorticated animals, and especially the marked recovery of movements of the face and extremities of Gardner's (1933) patient with a hemidecortication, all point to the same conclusion. In

addition it is difficult to explain the motor activity observed in some of our animals with complete bilateral extirpations of the motor and premotor areas (in which terminal stimulation did not yield the responses seen during the period of observation) unless one admits some subcortical activity.

## VI. SUMMARY

1. The clinical pictures of monkeys with unilateral or bilateral ablation of area 4c, or the lower part of 6a $\alpha$ , 6b $\alpha$  and 6b $\beta$ , or both are described.

2. From these observations plus those of the stimulation experiments (Walker and Green, 1938) it is concluded that: (a) Area 4 contains the direct cortical projections to the labial muscles, the orbicularis oculi, the buccal food pouches, and to the intrinsic muscles of the tongue; (b) Area 6a $\alpha$  (face) probably normally influences the activity of area 4c, but has itself few direct motor projections; (c) Area 6b $\alpha$  possesses independent projections which are mainly concerned with gross and frequently rhythmic movements, particularly of the tongue, functions which may be in part carried out by area 4, but more especially by subcortical structures; (d) The projections from area 6b $\beta$  are likewise independent of those of area 4 and serve to modify the activity of the respiratory center.

3. The lower facial musculature (lips and buccal pouch) is represented almost solely in the contralateral cortex, while the upper facial, lingual, pharyngeal and laryngeal muscles are to a considerable extent bilaterally represented.

4. Despite the bilateral representation of the lingual musculature, deviation and rotation of the organ towards a particular side are primarily controlled by a single area 4c, that of the homolateral hemisphere.

5. In the monkey the control of these various muscles is encephalized in descending order as follows: almost completely—lower facial (lips and buccal pouch) and lingual muscles, less marked—laryngeal and pharyngeal muscles, and least the upper facial muscles.

6. The factors responsible for recovery of motility after ablation of the cortical face motor and premotor area are, in order of importance: (a) remaining ipsilateral cortex of the motor or premotor face area; (b) contralateral motor and premotor cortex of the face region; (c) subcortical structures; (d) other cortical areas, sensory, prefrontal, etc.

The authors wish to express their appreciation to Professor J. F. Fulton for his many helpful suggestions and criticisms during the pursuit of this research.

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# CELL-CHANGES IN SOME OF THE HYPOTHALAMIC NUCLEI IN EXPERIMENTAL FEVER

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SEVERAL investigators have produced evidence to show that the hypothalamus plays an important role in the regulation of body temperature (Isenschmidt and Krehl;<sup>1</sup> Jakoby and Roemer,<sup>2</sup> Reichard;<sup>3</sup> Glaser,<sup>4</sup> Citrone and Leschke,<sup>5</sup> Barbour and Wing,<sup>6</sup> Morgan and Johnson;<sup>10</sup> Keller and Hare;<sup>11</sup> Bazett, Alpers and Erb;<sup>12</sup> Ranson and Ingram;<sup>13</sup> Frazier, Alpers and Lewy,<sup>14</sup> and others). However it has not yet been shown which nuclei of the hypothalamus are concerned with temperature regulation. Likewise the manner in which these nuclei influence body temperature and the physiological mechanisms involved are as yet not definitely understood.

The physiology of temperature regulation has been reviewed by Barbour.<sup>15</sup> The adrenal and thyroid glands and the hypophysis are believed to influence body temperature. Carbohydrate, protein and fat metabolism, the rate of evaporation of water from the body, peripheral vasomotor changes, changes in water and salt balance, water shifting and changes in blood sugar are believed to play an important role in regulating body temperature. The relationship of vegetative centers in the hypothalamus to several of these functions has been discussed in a previous paper.<sup>16</sup> The significance of this relationship to the regulation of body temperature has been discussed by Davison and Selby.<sup>17</sup>

It has been previously pointed out<sup>18</sup> that in mammals the cells of the nuclei of the hypothalamus are so intermingled that it is virtually impossible to place an experimental lesion in a single nucleus without causing injury to one or more adjacent cell groups. Furthermore our knowledge of the fiber connections in and through this region is not sufficient to preclude the possible effects of injury to fiber tracts when placing lesions in this area. The present investigation was undertaken with the hope that a fever producing substance such as typhoid toxin, might set up a reaction in the temperature regulating centers of the brain to the extent that the cells involved would show cytological alterations.

## METHODS

Fifteen dogs and four rabbits were used in this series of experiments. The procedure consisted essentially in producing an experimental hyperthermia by the injection of typhoid or bronchisepticus toxin. In all but two cases, typhoid toxin was used. The toxins were prepared for me from killed cultures of bacteria by Drs. Eddy and Howard in the Department of Bacteriology. The typhoid toxin was much stronger than the preparations commonly used for producing immunity in the human. Hypodermic injections were used in all but four cases. In these four animals (Nos. 10-13) the toxin was injected into a vein. The number of injections, the amount of toxin injected, and the period of time during which the injections were continued was varied considerably with different animals. Temperatures were taken by rectum with a clinical thermometer. One or more temperature readings were taken at frequent intervals for a period of hours after the injection until the temperature had risen and then returned to normal.

The accompanying table gives a summary of the most important data concerning the experimental procedure. The maximum rise in temperature recorded in the table represents the maximum rise in temperature which occurred after any single injection of toxin. The data indicate that rabbits are sensitive to much smaller doses of toxin, in proportion to body weight, than are dogs. It will also be noted that 0.6 cc. of toxin injected intravenously (cases 10-13) produced a greater rise in temperature in dogs than was usually obtained by a hypodermic injection of 4-10 cc.

A few hours after the last injection the animal was killed and the brain removed. The brain stem was embedded in celloidin and cut into sections 35 microns in thickness. These

Table I—Summary of Experiments

Animal Number	Size of Animal	Total of Toxin Injected	Number of Injections	Duration of Experiment	Maximum Rise in Temperature	Percentage of Chromatolytic Cells		
						Nucleus Tubero-mamm	Basal Optic Ganglia	Nucleus Paraventricularis
Dog 1	Small	16.5 cc.	5	72 hrs.	2.0°F.	50	14	13
Dog 2	Small	11.5 cc.	4	24 hrs.	2.2°F.	68	12	11
Dog 3	Large	20 cc.	4	24 hrs.	2.5°F.	56	22	18
Dog 4	Medium	15 cc.	4	24 hrs.	3.4°F.	57	0	0
Dog 5	Medium	21 cc.	4	24 hrs.	4.3°F.	51	20	12
Dog 6	Small	19 cc.	2	12 hrs.	1.2°F.	68	32	20
Dog 7	Large	23 cc.	2	12 hrs.	2.6°F.	68	9	8
Dog 8	Medium	24 cc.	2	12 hrs.	2.1°F.	66	6	6
Dog 9	Small	22 cc.	2	12 hrs.	3.8°M.	50	8	8
Dog 10	Medium	2.7 cc. intraven.	5	53 hrs.	5.2°F.	74	13	12
Dog 11	Medium	2.9 cc. intraven.	5	54 hrs.	4.0°F.	62	23	19
Dog 12	Medium	3.8 cc. intraven.	6	101 hrs.	3.2°F.	73	30	23
Dog 13	Large	3.8 cc. intraven.	6	101 hrs.	4.5°F.	33	12	12
Rabbit 14	Large	0.7 cc.	2	13 hrs.	4.5°M.	75	0	0
Rabbit 15	Large	1 cc.	2	14 hrs.	5.4°F.	77	—	—
Rabbit 16	Large	0.4 cc.	1	12 hrs.	1.7°F.	60	10	10
Rabbit 17	Large	0.4 cc.	1	10 hrs.	1.5°F.	56	0	0
Dog 18	Large	10 cc.	2	7 hrs.	4.1°F.	54	0	0
Dog 19	Large	B.Bronch. 16 cc.	2	23 hrs. Average	2.0°F.	43 60	10 15.8	5 12.6

sections were stained by a modified iron hematoxylin technique (Morgan)<sup>16</sup>. The sections were studied with the object of determining whether the toxins injected produced histological changes in any of the cell groups of the brain stem. In four cases a study was made of the entire brain stem from the caudal end of the medulla to the optic chiasma. In the remaining cases particular attention was given only to the region of the third ventricle, corpus striatum, thalamus, hypothalamus, epithalamus and mid-brain. The twenty brains previously used for a study of the normal histology of the hypothalamus in the dog (Morgan)<sup>18</sup> were used as controls.

## RESULTS

In so far as chromatolysis of nerve cells can be taken as a criterion, it is apparent that typhoid and bronchisepticus toxins have a selective action upon three cell groups all of which are located in the region of the third ventricle. The three cell groups which show definite chromatolytic changes are the nucleus tuberomammillaris (mammillo-infundibularis), the basal optic ganglia

(nucleus supra-opticus), and the nucleus paraventricularis. I have described and illustrated these cell groups in the brain of the dog in a previous paper,<sup>18</sup> and pointed out the differences in distribution of these cell groups in the dog, the albino rat, and the human.

The nucleus tubero-mammillaris is composed of large cells most of which are grouped around the fornix from the level of the optic chiasma to the mammillary bodies. The cells increase in number as we pass from the chiasma toward the mammillary bodies and smaller groups of cells are placed along the base of the tuber cinereum. The basal optic ganglia consist of large cells which

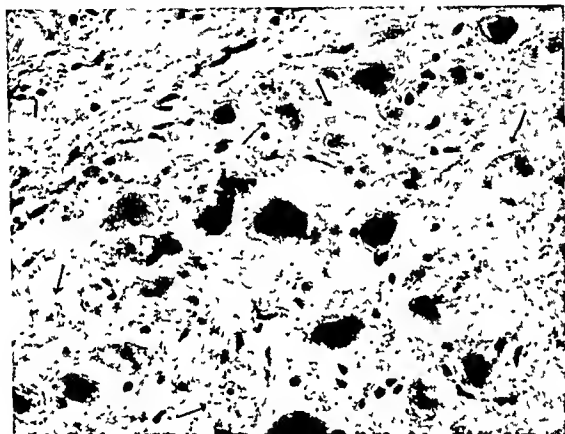


FIG 1 Photograph of a portion of the nucleus tubero-mammillaris (case 2) illustrating the cell changes which occur with experimental fever. The arrows indicate chromatolytic cells.

begin at the optic chiasma and extend for a short distance along the optic tracts. The nucleus consists essentially of two parallel columns of cells. The larger of these columns is placed along the dorsal portion of the oro-lateral surface of the optic tract. The second group of cells follow the caudo-medial border of the optic tract. The paraventricular nucleus is composed of large cells arranged in a column whose axis is almost perpendicular to that of the basal optic ganglion. This cell group begins near the oral end of the basal optic ganglion and extends upward and orally through the wall of the third ventricle toward the anterior commissure.

That the nucleus tubero-mammillaris, basal optic ganglia, and nucleus paraventricularis are quite sensitive to typhoid and bronchisepticus toxins, is indicated by the fact that one or two injections of these toxins is capable of producing marked chromatolysis in these cell groups within a few hours' time.



On the other hand, it is of interest to note that in those cases in which a larger number of injections was made over a longer period of time, there is no significant difference in the amount of chromatolysis.

The nucleus tubero-mammillaris was involved in every case and to a greater degree than either the basal optic ganglia or the nucleus paraventricularis. The number of cells in this nucleus which were definitely chromatolytic varied from 33 to 77 per cent (Fig. 1).

In many cases there is a striking similarity in the amount of chromatolysis found in the basal optic ganglia and the paraventricular nucleus. In those cases where there is a difference the basal optic ganglia are affected to a greater degree. In four cases neither of these nuclei possessed any cells which appeared definitely chromatolytic. In five cases 10 per cent or less of the cells were chromatolytic. The highest percentage of chromatolysis found in any case was 32 per cent for the basal optic ganglia and 23 per cent for the nucleus paraventricularis.

When we take an average of the amount of chromatolysis found in each cell group throughout the series of experiments the average number of chromatolytic cells in the nucleus tubero-mammillaris is 60 per cent of the total, for the basal optic ganglia 15.8 per cent, and for the nucleus paraventricularis there was an average of 12.6 per cent showing chromatolysis. Many cells showed variations from the normal appearance sufficient to suggest a tendency toward chromatolysis but unless the cell was definitely chromatolytic it was considered as normal.

An attempt was made to determine the role of the thyroids in producing hyperthermia in those animals injected with toxin. In seven of these cases the blood supply to the thyroids was clamped while the temperature was elevated. These animals were etherized and several readings taken until the temperature became stable. When the thyroids were clamped off the temperature fell rapidly. In a few cases the temperature fell to normal or below, but in most cases the temperature did not return entirely to normal. While these experiments indicate that the thyroids play some role in the production of hyperthermia in these cases there are apparently other factors involved. In rabbits Nos. 16 and 17 the thyroid glands were removed three days before the toxin was injected.

The evidence obtained from this investigation points to the nucleus tubero-mammillaris as playing an important role in the producing hyperthermia. The paraventricular nucleus and basal optic ganglia are implicated to a more variable and a lesser degree. However, the regulation of body temperature is so inseparably linked up with other somatic and vegetative functions that it is doubtful if we are justified at present in assuming the presence in the brain of a center which is solely concerned with the regulation of body temperature. If such a center exists it is probably closely associated with various vegetative centers in the hypothalamus thus utilizing several older, well established mechanisms which serve other functions in addition to playing a role in the regulation of body temperature.

## SUMMARY

The entire brain stem was studied in 15 dogs and 4 rabbits following an experimental fever produced by either a hypodermic or intravenous injection of either typhoid or bronchisepticus toxin.

Significant cell changes were noted only in three nuclei of the hypothalamus

The nucleus tubero-mammillaris was involved in every case. An average of 60 per cent of the cells in this nucleus showed definite chromatolytic change.

A variable amount of chromatolysis was found in the paraventricular nucleus and the basal optic ganglia in 14 of the 19 animals studied. The average number of chromatolytic cells in these cases was 15.8 per cent for the paraventricular nucleus and 12.6 per cent for the basal optic ganglia.

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# ZUR ELEKTRODENANORDNUNG BEI DEN REGISTRIERUNGEN BIOELEKTRISCHER POTENTIALSCHWANKUNGEN DER HIRNRINDE\*

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## I EINLEITUNG

NACHDEM in den letzten Jahren ein grösseres Material über die lokalisierten bioelektrischen Erscheinungen der Hirnrinde<sup>†</sup> gesammelt worden ist, ist es an der Zeit, eine weitere Analyse des Kurvenbildes anzustreben. Damit soll in der vorliegenden Mitteilung begonnen werden.

Folgende Arten von Ableitungen finden beim Studium der bioelektrischen Erscheinungen des Gehirns Verwendung.

1 Die enge bipolare Ableitung. Diese besteht darin, dass man beide Elektroden knapp nebeneinander auf die Hirnrinde legt oder dass man mittels einer konzentrischen Elektrode ableitet.

2 Die unipolare Ableitung. Bei dieser wird die differente Elektrode auf die abzuleitende Hirnrindenstelle und die indifferente auf eine Stelle des Schädels, welche selbst keine bioelektrischen Erscheinungen aufweist, gelegt. Dafür kommt der Schädelsknochen in Frage, z. B. das blossliegende Stirn- und Nasenbein und die *Protuberantia occipitalis externa*.

Diese beiden Ableitungsarten sind für lokalisatorische Fragen geeignet. Die Beziehungen zwischen den Kurvenbildern, die diese beiden Ableitarten ergeben, sollen hier in erster Linie untersucht werden.

3. Die Ableitung nach Berger, bei welcher bekanntlich die beiden Elektroden entweder auf Stirn und Hinterhaupt oder aber bitemporal gelegt werden. Diese Ableitung erfolgt in der Regel von der Oberfläche der Kopfschwarte.

Nach viel verbreiteten Auffassungen sind für die beiden erstgenannten Ableitungsarten folgende Vorteile und Nachteile zu erwarten.

Die enge bipolare Ableitung hat vor allem den Vorteil, dass sie die grösste Gewähr dafür gibt, dass nur die Potentialschwankungen der zwischen den Elektroden liegenden Hirnpartien registriert werden. Aus morphologischen wie physikalischen Gründen war anzunehmen, dass eng benachbarte Stellen mehr oder weniger gleichzeitig erregt werden können, so dass zwischen diesen Stellen kein grosses Potentialgefälle erwartet werden kann. Bei zu engem Elektrodenabstand werden ja auch die Amplituden der elektrischen Potentialschwankungen sehr klein, so dass sie sich von dem Störspiegel des Apparates eventuell nicht genügend abheben. Die Schwankungen grosser Amplitude, die das Summationsprodukt der Spannungspro-

\* Mit Unterstützung der Rockefeller Foundation.

† Siehe A. E. Kornmüller, 1937(a).<sup>1</sup>

duktion vieler Elemente darstellen, sind über bestimmten Feldern, z.B. der *Area striata*, innerhalb grösserer Strecken mehr oder weniger synchron in ihrem Verlauf, wie die unipolare Ableitung ergibt. Sie werden darum bei enger bipolarer Ableitung mit kleinsten Elektrodenabständen kaum registriert. Dafür beherrschen kleine rasche Schwankungen das Bild. Dabei könnte es sich um die erwähnten Einzelentladungen handeln. Grössere Elektrodenabstände bei der bipolaren Ableitung bringen wiederum die Gefahr mit sich, dass die Elektroden gleichzeitig von strukturell (architektonisch) differenten Gebieten ableiten. Dies gilt besonders dann, wenn im Bereiche kleiner architektonischer Felder, wie sie z.B. am Kaninchen zahlreich sind, oder in der Nähe architektonischer Grenzen abgeleitet wird. Die Lage der Elektroden in bezug zur architektonischen Gliederung der Hirnrinde muss aber unter allen Umständen festgestellt werden, wenn man bioelektrische Untersuchungen auf der Hirnrinde anstellt (Kornmüller 1932-37). Leider wurde dies auch von Adrian und Matthews nicht in Rechnung gezogen bei ihrem wertvollen Ansatz, eine Analyse des Elektrenkephalogramms auch an Hand von Untersuchungen an Tieren durchzuführen, wobei sie auch Befunde über die Abhängigkeit des Kurvenbildes von der Elektrodenlage bei bioelektrischen Untersuchungen auf der Hirnrinde mitgeteilt haben.

Die unipolare Ableitung hat den Vorteil, dass sie im allgemeinen Schwankungen grösserer Amplitude als die enge bipolare Ableitung ergibt, so dass man leichter oberhalb des Störspiegels der Apparatur arbeiten kann. Ferner hat die unipolare Ableitung den Vorteil, dass es natürlich viel leichter gelingt, eine einzelne Elektrode in ein bestimmtes architektonisches Feld zu legen als zwei Elektroden. Ob diese Ableitungsart den Mangel hat, dass die erhaltenen Kurven nicht nur von der Auflagestelle der differenten Elektrode, sondern auch von dem Gewebe zwischen differenter und indifferenten Elektrode stammen, soll uns hier in erster Linie beschäftigen.

## II. METHODIK

Die Untersuchungen zur vorliegenden Mitteilung wurden an Kaninchen durchgeführt. Ihre Befunde sind an folgende Voraussetzungen geknüpft:

Die Kopfschwarte und der Knochen sind in einem möglichst grossen Bereiche von den Hirnableitestellen entfernt, und die Dura ist zurückgeschlagen. Es liegt mindestens von einer Hemisphäre nahezu die gesamte dorsale Konvexität frei. Die Ableitungen erfolgen durch Auflegen der Elektroden auf die Hirnrinde und nicht durch Einstechen. Die "indifferente" Elektrode muss tatsächlich frei von elektrischen Potentialschwankungen sein. Sie hat möglichst weit vom Gehirn wie auch von anderem bioelektrisch aktiven Gewebe, z.B. Muskeln, entfernt zu liegen und darf auch keine gut leitenden Verbindungen, z.B. durch Kochsalzlösung, zu solchen Geweben haben.

Des weiteren soll noch auf einige andere methodische Besonderheiten hingewiesen werden:

Zur Ableitung wurden überwiegend die im folgenden beschriebenen Metallelektroden benutzt, die sich durch kontrollierbaren Auflage-  
druck und durch zuverlässige Kontaktgabe auszeichnen. Siehe Fig. 1!

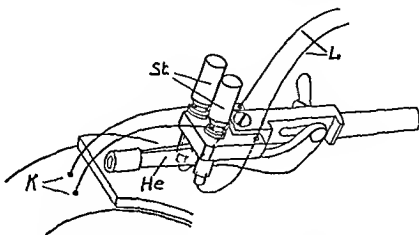


Fig. 1. Metallelektrode Beschreibung im Text.

Ein mikrometrisch verstellbares Stativ trägt den Elektrodenhalter. Dieser besteht aus einem Vierkanteisen und einer daran festgeschraubten Presstoffplatte, in die zwei Messingbuchsen eingesetzt sind. An ihnen sind die Zuleitungen *L* angelotet. In die Buchsen werden kleine Stecker *St* gesteckt, an denen Messingdrähte von 0,2 mm  $\phi$  angelotet sind, die am freien Ende angeschmolzene Silberkugeln *K*, von 1,5 mm  $\phi$  tragen. Von einem galvanischen Überziehen dieser Kugeln, die die eigentlichen Auflageelektroden darstellen, mit AgCl wurde abgesehen, da aus den weiter unten dargelegten Gründen nicht mit der Wirkung von Polarisationsspannungen zu rechnen war, was sich bei den Versuchen durchaus bestätigte. Der Druck, mit dem die sehr weich federnden Messingdrähte die Silberkugeln auf das blossliegende Gehirn anlegen, betrug bei den in Betracht kommenden Durchbiegungen der Drähte ca. 0,1 g. Demnach war der entsprechende Flachendruck bei einer Auflagefläche von 3,5 mm<sup>2</sup> pro Kugel 0,03 g/mm<sup>2</sup>. Natürlich hängt dieser Druck von dem Grade der Durchbiegung ab. Um nun bei plötzlicher Unruhe des Versuchstieres zu verhindern, dass die Elektroden die Hirnoberfläche verletzen, wurde an dem Elektrodenhalter ein einstellbarer, am Ende mit Gummischlauch überzogener Hebel *He* angebracht, der am Rande der Trepanationsöffnung dem stehengebliebenen Schädelsknochen aufliegt, wenn gleichzeitig die Elektroden mit dem zulässigen Druck das freiliegende Gehirn berühren. Bei Unruhe des Tieres wird dann die gesamte Elektrodenanordnung angehoben, ohne dass sich der Druck auf das Gehirn ändert. Da die eigentlichen Elektroden nur durch ihre Stecker mit den Zuleitungen verbunden sind, ist die Auswechslung gegen Elektroden mit anderen Ausmassen oder die Ersetzung von beschädigten Elektroden ohne Zeitverlust möglich.

Als indifferenten Elektroden dienten Tontiefel oder einfache Metallelektroden.

Zur Verstärkung der bioelektrischen Erscheinungen dienten drei C-W-gekoppelte Verstärkersätze des von Tonnies (1935) konstruierten Polyneurographen, vor deren Eingangsstufen drei Differentialverstärker nach Tonnies\* geschaltet waren.

Diese Differentialverstärker haben je drei Eingangsklemmen (a, b, E auf Fig. 2) und zwei Ausgangsklemmen, die zum Gitter und zur Kathode der nachfolgenden Verstärkerstufe, d. h. der jeweils ersten Stufe im Polyneurographen, führen. Durch die besondere Schaltung des Differentialverstärkers, die eine modifizierte Gegentaktschaltung darstellt, ist erreicht, dass gemeinsame Aussteuerungen von a und b

\* Noch nicht veröffentlicht.

gegenüber E sich mit weniger als 1/1000 in der registrierten Kurve auswirken, verglichen mit einer gleich grossen Aussteuerung zwischen a und b. Dadurch werden aus dem Wechselstromnetz herrührende Störungen, die die mit a und b verbundenen Elektroden praktisch gleichmässig beeinflussen, sehr weitgehend vermindert. Es muss lediglich auf die gute Kontaktgabe der mit E verbundenen Elektrode geachtet werden, die zur Ableitung der Störungen nach der Erde dient. Sie wird im folgenden als E- (Erdungs-) Elektrode bezeichnet und ist nicht zu verwechseln mit der „indifferenten“ Elektrode der unipolaren Ableitung. Potentialschwankungen unter der E-Elektrode allein wirken sich praktisch nicht auf den Ableitkreis aus, während sich Spannungsschwankungen, die eventuell unter der „indifferenten“ Elektrode auftreten, selbstverständlich voll auswirken. Die Klemmen a und b jedes Differentialverstärkers gehen unmittelbar, d.h. ohne zwischengeschaltete Kondensatoren, an die Gitter der zugehörigen Verstärkerröhren, die im übrigen keine leitenden Verbindungen mit den Kathoden, d.h. keine eingebauten Gitterwiderstände haben. Die Aussteuerung der beiden Gitter erfolgt also rein statisch, ohne dass die abgeleiteten Spannungen durch einen Gitterwiderstand belastet werden. Dadurch ist das Fließen eines Stromes im Ableitkreis unmöglich, so dass auch die Ausbildung von störenden Polarisierungsspannungen mit Sicherheit verhindert ist. Die Verwendung von „unpolarisierbaren“ Elektroden ist dadurch überflüssig, und deshalb konnten die oben beschriebenen sehr einfach herzustellenden und mechanisch unempfindlichen Metallelektroden ohne Nachteil verwendet werden.

Wird einer der beschriebenen Differentialverstärker zur bipolaren Ableitung benutzt, dann wird die eine der differentiellen Elektroden mit a und die andere mit b verbunden. Siehe Fig. 2! Als E-Elektrode verwenden wir eine grossflächige Klemme an einem Ohr.

Bei der unipolaren Ableitung kann entweder

α) a mit einer differentiellen und b mit einer indifferenten Elektrode (z.B. auf dem Nasenbein) verbunden werden. Die E-Elektrode des Differentialverstärkers liegt wie eben erwähnt. Oder

β) es wird auf die Trennung der indifferenten von der E-Elektrode verzichtet, d.h. beide werden gemeinsam genommen.

Für die Registrierung der bioelektrischen Spannungen sind die beiden unipolaren Ableitungsarten (α und β) vollkommen gleichwertig; nur für die Ausschaltung der Störungen besteht ein Unterschied, da bei der Schaltung nach β die Gegentaktwirkung aufgehoben und die Störanfälligkeit dadurch erhöht ist.

Für die in Abschnitt III, 2 dieser Mitteilung beschriebene Versuchsreihe war es nötig, mit den vorhandenen Mitteln eine Schaltung der Verstärker zu finden, die es ermöglicht, eine Kurve zu registrieren, welche die Differenz der Potentialschwankungen von zwei gleichzeitigen unipolaren Ableitungen darstellt. Dies wurde auf folgende Arten erzielt:

1. In der Fig. 2 stellen A, B und C schematisch drei Differentialverstärker dar, deren Eingangsklemmen wieder mit a, b und E bezeichnet sind. Auf dem Gehirn des Versuchstieres liegen die mit 1 und 2 gekennzeichneten differentiellen Elektroden; auf dem Nasenbein liegt die indifferente Elektrode N. Am Ohr des Tieres ist eine Klemme O befestigt als E-Elektrode. Im Verstärker C wird die Potentialdifferenz zwischen 1 und 2 verstärkt und auf den nachfolgenden Verstärkersatz übertragen; die Elektrode O dient hierbei nur zur Erdung und damit zur Ableitung der aufgenommenen Wechselstromstörungen. Die Elektrode 1 ist mit der Klemme a des Verstärkers A und die Elektrode 2 mit b von B verbunden, deren E-Klemmen gemeinsam mit der von C geerdet sind. Die noch freien Klemmen b von A und a von B sind gemeinsam mit der indifferenten Elektrode N

verbunden. Die Verstärker A und B erhalten also als Aussteuerung die Potentialdifferenz zwischen 1 und N bzw. N und 2 in unipolarer Ableitung. Die in A und B verstärkten Spannungsschwankungen werden gemeinsam auf das Gitter einer nachfolgenden Stufe gegeben. Da A und B hierbei so geschaltet sind, dass eine gemeinsame Spannungsänderung an 1 und 2 sich in dem zusammengeschalteten Ausgang aufhebt, so wirkt an diesem Ausgang tatsächlich die Differenz der unipolaren Ableitung zwischen 1 und N bzw. N und 2 als Aussteuerung.

2. Es können auch hier, wie oben unter 1 gesagt, die indifferente und die E-Elektrode gemeinsam genommen werden. Siehe die gestrichelte Linie zwischen a und E des Verstärkers B in Fig. 2!

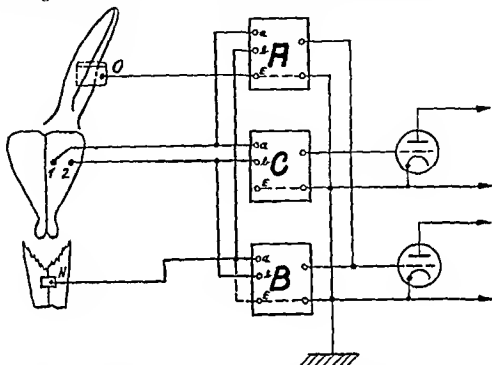


FIG. 2. Links: Lage der Elektroden am Tier. Rechts: Schaltung zur physikalischen Differenzbildung der Kurven von den unipolaren Ableitungen 1-N und 2-N und zur gleichzeitigen Registrierung der bipolaren Ableitung 1-2. Beschreibung im Text.

Die Registrierungen wurden mit den Tintenschreibern des Tonnie'schen Polyneurographen (lc) vorgenommen.

Geringfügige Abweichungen in der Aufzeichnung von Frequenzen um 50 Hertz erklären sich aus kleinen, während dieser Untersuchung bestehenden Differenzen zwischen den Dämpfungseigenschaften der einzelnen Schreiber. Diese Abweichungen traten auch auf, wenn eine gemeinsame Aussteuerung auf die drei benutzten Schreiber geschaltet wurde und erwiesen sich bei einer genaueren Durchmessung als physikalisch bedingt. So weit also bei dem Vergleich der elektrisch gewonnenen Differenz zweier unipolarer Ableitungen mit der zugehörigen bipolaren Ableitung derartige geringe Unterschiede auftreten, sind sie nach genauerer physikalischer Analyse durch die erwähnte Verschiedenheit der Schreiber-eigenschaften auch quantitativ vollkommen erklärt.\*

### III. ERGEBNISSE

#### 1. Unipolare Ableitungen mit verschiedener Lage der indifferenten Elektrode

Die Hirnstelle 1 wird, wie Fig. 3 zeigt, unipolar gleichzeitig I gegen die Protuberantia occipitalis externa (P) und II gegen das Stirnbein (S) abgeleitet.

\* Einzelheiten über die Frequenzeigenschaften der für die vorliegende Untersuchung benutzten Registrierung wird Schaefer demnächst im Rahmen einer Mitteilung über die Aufzeichnungsmethoden bioelektrischer Erscheinungen mit besonderer Berücksichtigung der Tintenschreibung angeben.



Diese beiden Kurven (I und II) sind erstaunlich parallel, und jede Einzelheit der einen Kurve ist auch an der anderen zu sehen. Das ist umso bemerkenswerter, als sich bei den Ableitungen für Kurve I und II morphologisch und entsprechend auch bioelektrisch unterschiedliche Hirngebiete zwischen dem gemeinsamen differenten und den verschiedenen indifferenten Punkten befinden. Dies soll die gleichzeitig registrierte Kurve III, eine bipolare Ableitung von der Area praecentralis granularis (2-3 in

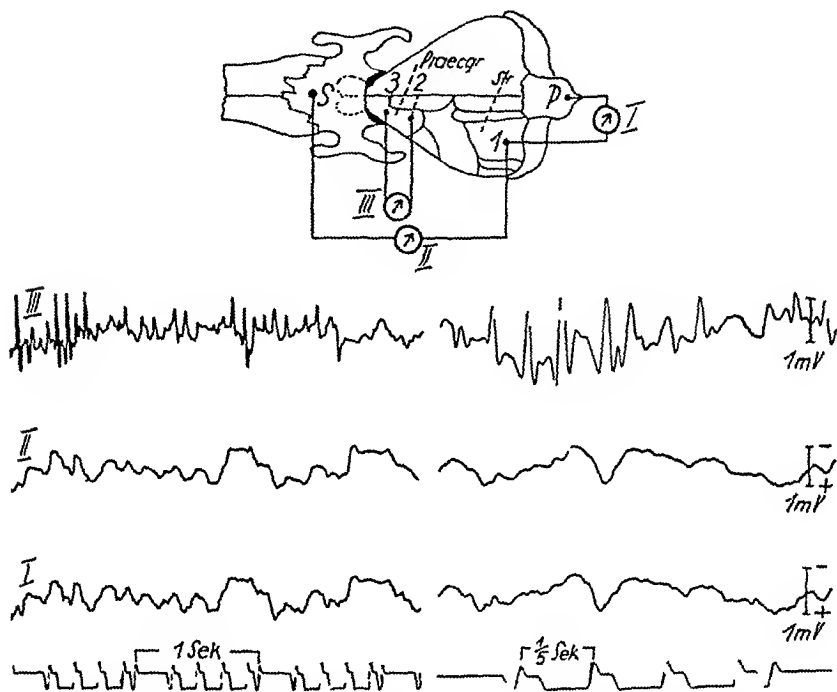


FIG. 3. Oben: Grosshirn und Teile des knöchernen Schädels eines Kaninchens, von oben gesehen. Auf der linken Hemisphäre schematisch die architektonische Rindengliederung.

Unten: Gleichzeitige Ableitung von

- I: 1-P
- II: 1-S
- III: 2-3

Praecgr), zeigen. Das genannte Feld, dessen Eigenströme u.a. durch Gruppen rascher Schwankungen (12-15 Hz) gekennzeichnet sind, liegt breit über der Verbindungslinie der Punkte 1 und S, also zwischen den Ableitelektroden der Kurve II. Trotzdem lässt die Kurve II nichts von diesem raschen Rhythmus erkennen.

Nach dem in Fig. 3 dargestellten Prinzip wurde unter Beibehaltung der angegebenen Lagen für die indifferenten Elektroden unipolar über den verschiedensten Stellen der Hirnrinde abgeleitet. Dieses Material führte zu dem gleichen Befunde, wie das angegebene Beispiel, nämlich:

Die Kurvenform der unipolaren Registrierungen der bioelektrischen Erscheinungen je einer Hirnrindenstelle ist unabhängig von der Lage der indifferenten Elektrode.

## 2. Gleichzeitige unipolare und bipolare Ableitungen von zwei Rindenstellen

Von den Hirnrindenstellen 1 und 2 der Fig. 4 wird gleichzeitig folgendermassen abgeleitet (siehe A der Fig. 4): I zwischen 1 und 2, II zwischen 2 und der Protuberantia occipitalis externa (P) und III zwischen 1 und Nasenbein (N). Wenn sich auf den Ableitkreis tatsächlich nur die Potentialschwankungen auswirken sollten, die in unmittelbarer Nähe der Elektroden auftreten und nicht die bioelektrisch aktiven Gebiete zwischen den Elektroden, dann müsste die Kurve der bipolaren Ableitung (1-2) gleich sein der Differenz\* der beiden unipolaren Registrierungen (1-N und 2-P). Es wurden in diesem Falle mit Absicht für die beiden unipolaren Ableitungen verschiedene indifferente Elektrodenlagen (N und P) gewählt, damit die bioelektrisch aktiven Gebiete zwischen den Elektrodenpaaren der unipolaren Ableitungen verschieden sind. Nur so lässt sich mit Bestimmtheit die Frage beantworten, ob die bipolare Ableitung gleich ist der Differenz der beiden unipolaren Ableitungen. Andernfalls nämlich konnte sich eine gemeinsame Strecke zwischen den Elektrodenpaaren der unipolaren Ableitungen zufolge einer gemeinsamen indifferenten Elektrode vorfinden und die Subtraktion gleicher Einwirkungen auf beide unipolare Ableitkreise würde die bipolare Ableitung ergeben, obgleich sich in diesen Fällen das zwischen den differenten Stellen und dem gemeinsamen indifferenten Punkt liegende Gewebe doch auf den Ableitkreis auswirken könnte. Die Differenz zwischen den Potentialschwankungen zweier verschiedener Ableitungen wurde in der im methodischen Teil dargelegten Weise direkt ermittelt. Siehe Fig. 2! Das Ergebnis zeigen die Streifen B und C der Fig. 4. B I und C I stellen bipolare Registrierungen zwischen den Punkten 1 und 2 dar. Die Kurven B, III-II und C, III-II sind die Differenzen zwischen den Potentialschwankungen der unipolaren Ableitungen 1-N und 2-P. Die Figur zeigt deutlich, dass die Kurvenform der bipolaren Ableitung (I) gleich ist den Kurven, die die Differenz der beiden unipolaren Ableitungen (III-II) darstellen. Es muss ausdrücklich bemerkt werden, dass alle Kontrollmöglichkeiten erschöpft wurden, die die Unabhängigkeit der bipolaren Ableitung von den Ableitungen der Differenzkurven erwiesen.

Ausser auf diesem physikalischen Wege wurden auch geometrische Subtraktionen von gleichzeitig registrierten unipolaren Kurven vorgenommen. Die so konstruierte Kurve war immer und für alle Einzelheiten völlig identisch mit der gleichzeitig registrierten bipolaren Kurve. Da letztere Kurve keine zusätzlichen Schwankungen aufweist, lässt sich auch aus dieser Versuchsreihe folgern, dass sich das Gewebe zwischen den Elektroden nicht

\* Die Polartaten sind an den Eichstrichen ersichtlich

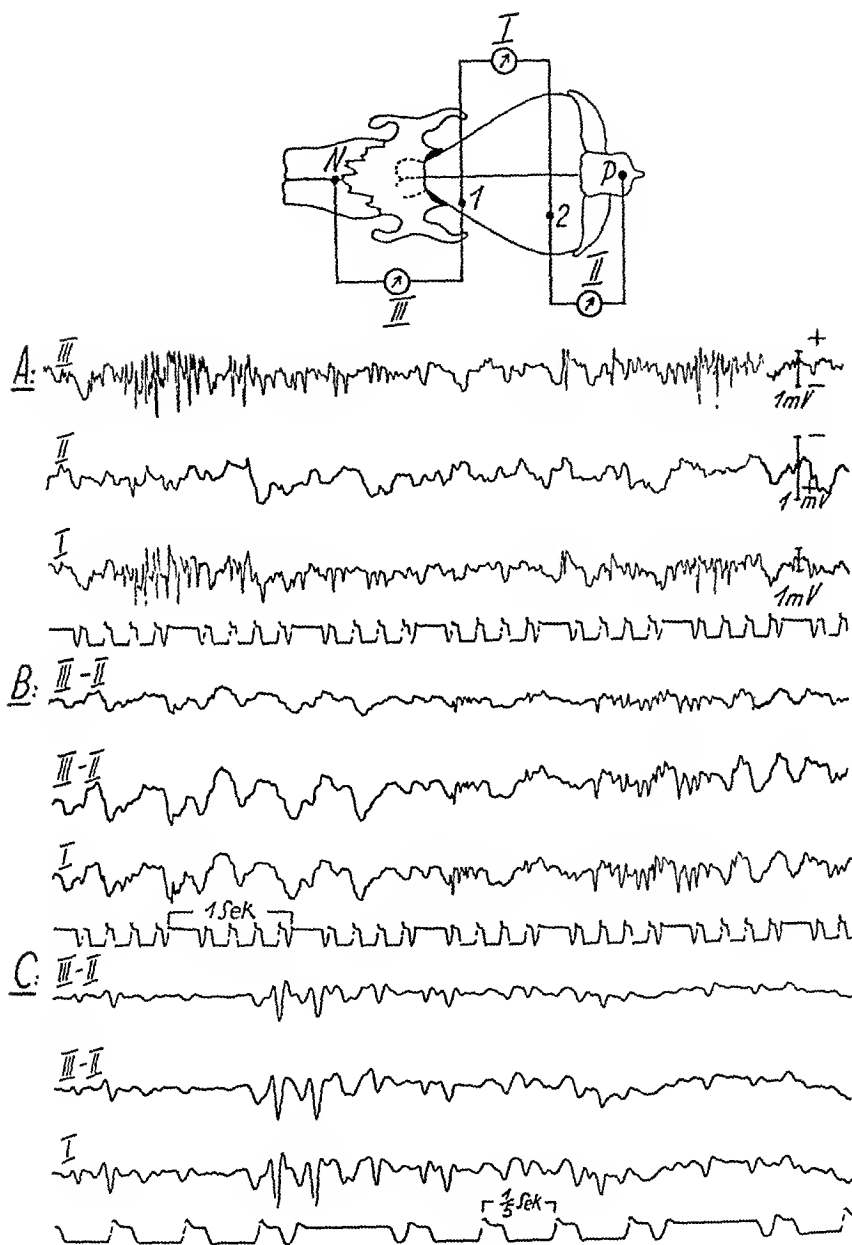


FIG. 4. Gleichzeitige Ableitung von

A:

I: 1-2  
 II: 2-P  
 III: 1-N

B und C:

I: 1-2  
 III-II: Differenz von (1-N) und (2-P)

merkbar auf den Ableitekreis auswirkt. Dass dies selbstverständlich nur unter den in der Methodik aufgezeigten Voraussetzungen gilt, brauchte nicht noch einmal hervorgehoben zu werden.

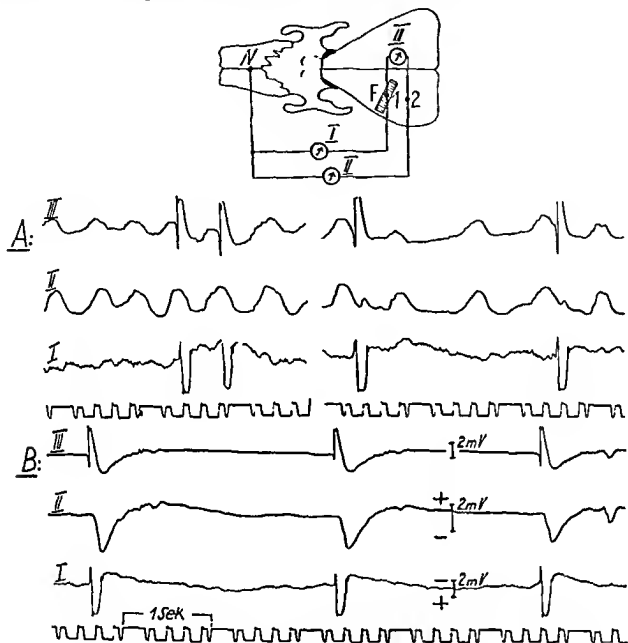


FIG. 5. Gleichzeitige Ableitung von

I: 1-N

II: 2-N

III: 1-2

F=Filterpapier mit Strychnin.

### 3. Abnorm starke bioelektrische Potentialschwankungen (Krampfströme) auf der Strecke zwischen den Elektroden

Es wurde die in Fig. 5 (oben) dargestellte Elektrodenanordnung benutzt. Nach Strychninisation der Stelle 1 wurde von 1 und 2 gleichzeitig sowohl bipolar (A III) als auch von jedem einzelnen Punkte unipolar gegen das Nasenbein (N) abgeleitet: A I=1-N und A II=2-N. Alle Elektrodenauflagepunkte liegen auf einer Geraden. Die Krampfstromzacken über 1 sind nur auf der unipolaren Ableitung von Stelle 1 (A I) und auf der bipolaren

Ableitung 1-2 (A III) festzustellen. Die unipolare Ableitung von 2 (A II) lässt nichts von Krampfstromzacken erkennen, obgleich sie unweit davon und noch dazu zwischen den Elektroden vorhanden sind. Bei dieser Versuchsreihe wurden bei den einzelnen Tieren verschiedene Rindenstellen zwischen 2 und dem Nasenbein (N) strychninisiert, so dass die Gegenden mit Krampfströmen in den verschiedensten Abständen von den Punkten 2 und N lagen. Auf Streifen B der Fig. 5 kommen wir weiter unten zu sprechen.

Es wurden auch noch Abänderungen dieser Versuchsanordnung durchgeführt, z.B. folgende, die in Fig. 6 dargestellt ist: Es liegt je eine Elektrode auf dem Nasenbein (N), auf der *Area praecentralis granularis* (1), auf der *Area striata* (2) und auf der *Protuberantia occipitalis externa* (P). Nach einer Kontrollregistrierung und Strychninisation mittels eines Blättchens Filtrierpapier (F) von 2 wird I zwischen 1 und 2, II zwischen 2 und N und III zwischen 1 und P abgeleitet. Die Kurven I und II zeigen deutliche Krampfstromentladungen, Kurve III dagegen nicht, obgleich auch hier die Krampfstromentladungen zwischen den Elektroden dieser Ableitung sehr intensiv vorhanden sind. Nebenbei bemerkt zeigen diese dreifachen Registrierungen auch sehr schön, dass die bipolare Kurve (I) alle Wellen der beiden unipolaren, aber keine zusätzlichen Schwankungen erkennen lässt. Schon die grobe Betrachtung lässt erkennen, dass die Kurve der bipolaren Registrierung gleich ist der Differenz der beiden entsprechenden unipolaren Registrierungen.

In Ergänzung der Befunde der eben geschilderten Versuchsreihe muss noch darauf hingewiesen werden, dass nach länger dauernder Strychnineinwirkung auf die Stelle 1 der Fig. 5 und auf die Stelle 2 der Fig. 6 sich auch von den nicht strychninisierten differenten Ableitpunkten Krampfströme gelegentlich registrieren lassen. Ein Beispiel dafür zeigt B der Fig. 5:

Im Gegensatz zu A enthält hier die Ableitung II ebenfalls Krampfstromschwankungen. Diese aber haben eine andere Form als die der Ableitung I. Sie sind träger und weisen ausserdem bei grösserer Papiergeschwindigkeit eine deutliche Latenzzeit gegenüber den Krampfstromschwankungen von I auf. Die Latenzzeit betrug etwa 75  $\sigma$ . Der Abstand zwischen den Punkten 1 und 2 betrug 8 mm, das würde in diesem Falle eine Leitungsgeschwindigkeit von knapp über 100 mm pro Sekunde bedeuten. Es handelt sich hier also nicht um eine physikalische Streuung der grossen Potentialschwankungen der Stelle 1 auf die Elektrode der Stelle 2, sondern darum, dass sich die von Stelle 1 ausgehenden Erregungen auf Stelle 2 auswirken. Die Registrierung B III, die die gleichzeitig vorgenommene bipolare Ableitung darstellt, setzt sich aus den aufeinanderfolgenden Krampfstromschwankungen der beiden unipolaren Ableitungen I und II zusammen. Man wird, wenn man quantitative Unterschiede ausser Acht lässt, bei diesem Kurvenbild an das Verhalten der bipolaren Ableitung von Muskeln bzw. peripheren Nerven erinnert.



Die Erregungsausbreitung auf der Hirnrinde liess sich auf Grund der normalen Erscheinungen (Eigenströme) bisher nur in vereinzelten geeigneten Fällen feststellen (Kornmüller, z.B. 1933 und 1935(a)), weil es bei der Mannigfaltigkeit der ständig vorhandenen Potentialschwankungen oft schwer fällt, einander entsprechende Wellen verschiedener Ableitpunkte genau zu ermitteln. Kornmüller hat (1937(a)) kurz darauf hinweisen können, dass die transkortikale Ausbreitung abnorm starker Erregungen, wie sie sich wohl in den Krampfströmen anzeigen, in den differenten Rindenarealen verschieden sein kann und offenbar von den morphologischen Verbindungen tangentialer Richtung innerhalb der Hirnrinde abhängig ist. Inzwischen hat Adrian der Frage der Erregungsausbreitung über der Hirnrinde eine besondere Untersuchung gewidmet, in welcher er zu bemerkenswerten Befunden gekommen ist, deren Mitteilung in diesem Zusammenhang zu weit führen würde.

#### IV. BESPRECHUNG

Die hier mitgeteilten Befunde sind unseres Erachtens eindeutig und klar, wenn auch eine Ermittlung ihrer physikalischen Grundlagen noch nicht vorgenommen worden ist. Wir unterlassen es, hier diesbezügliche Auffassungen auszusprechen. Wenn diese Ergebnisse auch einigen Autoren selbstverständlich sein mögen, so ist uns andererseits bekannt, dass selbst manche Elektrobiologen sie nicht erwartet hätten. So ist z.B. an der unipolaren Ableitung vielfach Kritik geübt worden. Siehe die Einleitung! Nach den mitgeteilten Befunden ist aber sicher, dass die unipolare Rindenableitung vor der bipolaren entschieden Vorteile hat und dass die einleitend ausgesprochenen Bedenken gegen diese Ableitungsart nicht zu Recht bestehen. Trotzdem sind wir weiterhin der Auffassung, dass es zweckmässig ist, bei Untersuchungen über die bioelektrischen Erscheinungen des Gehirns nach Möglichkeit sowohl die unipolare als auch die bipolare Ableitung vorzunehmen (Kornmüller 1937(b)). Dies geschieht am besten durch gleichzeitige mehrfache Registrierungen. Auf Grund eines solchen Materials wird man in der Analyse der bioelektrischen Erscheinungen des Gehirns voraussichtlich leichter weiterkommen als auf Grund nur einer der beiden Ableitungsarten.

Die mitgeteilten Befunde gelten, wie gesagt, nur für den Fall, dass vom weit freigelegten Gehirn registriert wird. Die Ableitungen vom blossliegenden Gehirn sind aber unter allen Umständen viel mehr in der Lage, über das tatsächliche und unverfälschte bioelektrische Verhalten der Hirnrinde etwas auszusagen als Untersuchungen, bei denen durch die Kopfschwarte und den Knochen registriert wird. So ist anzunehmen, dass bei Registrierungen durch den uneröffneten Schädel die oben mitgeteilten eindeutigen Ergebnisse nicht zu gewinnen sind. Dieses zu prüfen, muss einer gesonderten Versuchsreihe vorbehalten bleiben. Keinesfalls aber ist es angängig, auf Grund von Befunden, die durch Ableitung vom uneröffneten Schädel gewonnen wurden, Ergebnisse zu bezweifeln, die durch direkte Rindenableitungen in jahrelangen Untersuchungen von verschiedenen Autoren immer wieder bestätigt wurden.

Berger schreibt z.B.: "Nun haben aber die schönen Versuche Ectors' ergeben, dass man auch beim Kaninchen unter der Einwirkung der verschiedensten Sinnesreize bei einer bipolaren Ableitung von der Rinde selbst mit 4-5 mm voneinander entfernten

Elektroden, und zwar im Bereich des zugehörigen Sinneszentrums keine Spannungszunahme der Potentialschwankungen, sondern dabei, wie ich es schon 1930 beim Menschen beschrieben habe, einen Spannungsabfall findet, indem die grossen  $\alpha$ -W. schwinden und durch kleinere kurze  $\beta$ -W. ersetzt werden." Wir bezweifeln nicht diesen Befund von Ectors, der nicht vom weit blossliegenden Gehirn gewonnen wurde, sprechen ihm aber völlig die Fähigkeit ab, die unzweifelhafte Tatsache zu widerlegen, dass bei direkter und morphologisch kontrollierter Ableitung von der *Area striata* sowohl bei unipolarer als auch bei bipolarer Elektrodenanordnung auf Augenbelichtung Steigerungen der bioelektrischen Spannungsproduktion im Sinne der Feldaktionsströme zu finden sind. Das gleiche gilt für die beschriebenen Areale, die auf andere Qualitäten von Sinnesreizen Aktionsströme produzieren.

So lange daher die besonderen physikalischen Verhältnisse der Ableitungen durch den uneröffneten Schädel (Berger) nicht restlos geklärt sind, erscheint es uns unberechtigt, die Ergebnisse der Untersuchungen über den Berger-Rhythmus mit denen der bioelektrischen Lokalisationsmethodik (Kornmüller 1932-1937) zu vermischen bzw. Befunden der direkten Hirnableitung entgegenzustellen, weil Ableitungen durch den Schädel nicht Gleiches ergeben haben. Andererseits sind wir aber davon überzeugt, dass sich in absehbarer Zeit Klarheit über das Verhältnis der bioelektrischen Bilder, die einerseits durch direkte Rindenableitung und andererseits vom uneröffneten Schädel gewonnen werden, ergeben wird.

Es muss noch ausdrücklich bemerkt werden, dass die oben mitgeteilten Befunde nur für das lebende Hirngewebe gelten und nicht für Hirntote, die tot (nekrotisch) sind oder teilweise grobe Schädigungen aufweisen. Einzelne Befunde, deren systematische Nachprüfung noch aussteht, veranlassen zu dieser Feststellung.

Ausserdem gilt das oben Mitgeteilte, weil nur dieses untersucht wurde, für die Grosseordnung der bioelektrischen Erscheinungen der Hirnrinde und für die zu deren Registrierung üblichen Empfindlichkeiten der Apparate. Selbstverständlich ist anzunehmen, dass sich grössere Spannungen als die genannten auch auf Elektroden, die in weiterer Entfernung liegen, auswirken, und schliesslich muss auch mit entsprechend grossen Empfindlichkeiten, die aber bei dem üblichen Versuch praktisch nicht gebraucht werden, eine Streuung entfernter liegender Punkte auf die Elektroden feststellbar sein. So haben Untersuchungen von Jung und Kornmüller, welche gleichzeitige mehrfache Ableitungen bioelektrischer Erscheinungen subkortikaler Kerne betreffen, wie an anderer Stelle ausgeführt wird\*, unter Umständen abweichende Befunde ergeben, was u.a. darauf zurückzuführen ist, dass die Grösseordnung der bioelektrischen Potentialschwankungen subkortikaler Kerne niedriger liegt als die der Hirnrinde.

## V. ZUSAMMENFASSUNG

Bei Ableitung von der weit blossliegenden Hirnrinde ist

1. das Kurvenbild der unipolaren Ableitungen unabhängig von der Lage

\* Erste Mitteilungen darüber erscheinen im *Zbl. Neurol.* (Vortrag in der Neurol.-Psychiatr. Ges. Berlin, Jan. 1938) und im *Arch. Psychiatr.*, 1938, 108.



der indifferenten Elektrode, obgleich bei verschiedener Lage dieser Elektrode morphologisch wie bioelektrisch unterschiedliche Hirngebiete zwischen den Ableitpunkten liegen.

2. Das Kurvenbild der bipolaren Ableitung ist gleich der Differenz der beiden unipolaren Kurven, die von den Punkten der bipolaren Ableitung gewonnen werden.

3. Selbst Krampfströme, die zwischen den beiden Elektroden einer Ableitung hervorgerufen werden, lassen unter den üblichen Bedingungen keine physikalische Streuung auf diese Elektroden erkennen.

Am Schluss werden die Befunde kurz besprochen.

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# THE INFLUENCE OF HYPOGLYCEMIA ON THE SENSITIVITY OF THE CENTRAL NERVOUS SYSTEM TO OXYGEN WANT\*

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## I. INTRODUCTION

IN AN earlier paper by Glickman and Gellhorn (1938) it was shown that rats when in hypoglycemia show an increased sensitivity to diminished barometric pressure. A mild degree of anoxia, which produces no symptoms at normal blood sugar levels, decreases the latent period for insulin convulsions, although the blood sugar at the time of convulsions is no lower than that associated with insulin convulsions in animals kept under normal atmospheric pressure. The experiments give added support to the anoxia theory of insulin convulsions. It is important to extend the observations to preconvulsive states in order to determine whether a subconvulsive lowering of the blood sugar is also accompanied by an increased sensitivity to low oxygen tensions. If this were the case substantial progress would be made in the understanding of the mechanism by which hypoglycemia affects the central nervous system. In order to test this hypothesis it is desirable to use a reaction, suitable for quantitative measurements, and one that is also dependent on the excitability of some part of the central nervous system. For this purpose the blood pressure response to low oxygen tension was chosen. Gasser and Loevenhart (1914), and later Heymans, Nowak and Samaan (1934) concluded that the rise in blood pressure accompanying the inhalation of air at a low oxygen tension is due to direct stimulation of the vasomotor center. Since the level of the blood pressure increases with decreasing oxygen tension, this reaction may be used for quantitative study. Recent experiments of Lambert and Gellhorn (1938), however, indicate that the rise in blood pressure during anoxia is due to *reflex* stimulation of the vasomotor center. For our considerations this new interpretation of the blood pressure rise occurring in anoxia is of little concern since the rise in blood pressure may be taken as a measure of sympathetic excitation, irrespective of whether the sympathetic center has been stimulated directly or reflexly. If the theory based on the work of Olmsted and Logan (1923), Olmsted and Taylor (1924), Holmes (1930), Wortis (1935), Dameshek and Myerson (1935), Loman and Myerson (1936), and Himwich and collaborators (1937) is correct, that a lowering of the blood sugar reduces both the sugar and oxygen con-

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† The material here presented has been abstracted in two preliminary papers by Moldavsky and Gellhorn (1937) and Ingraham, Moldavsky and Gellhorn (1937).

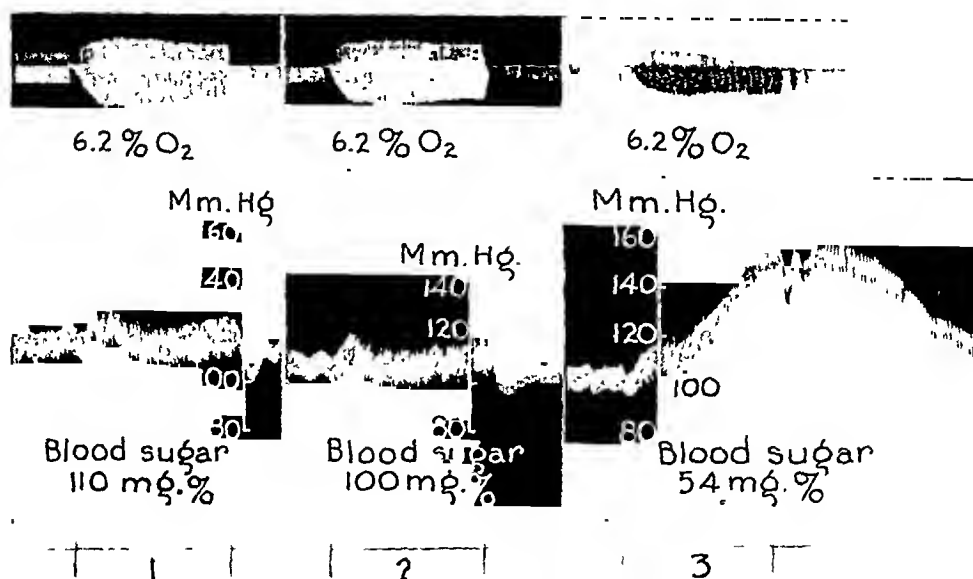
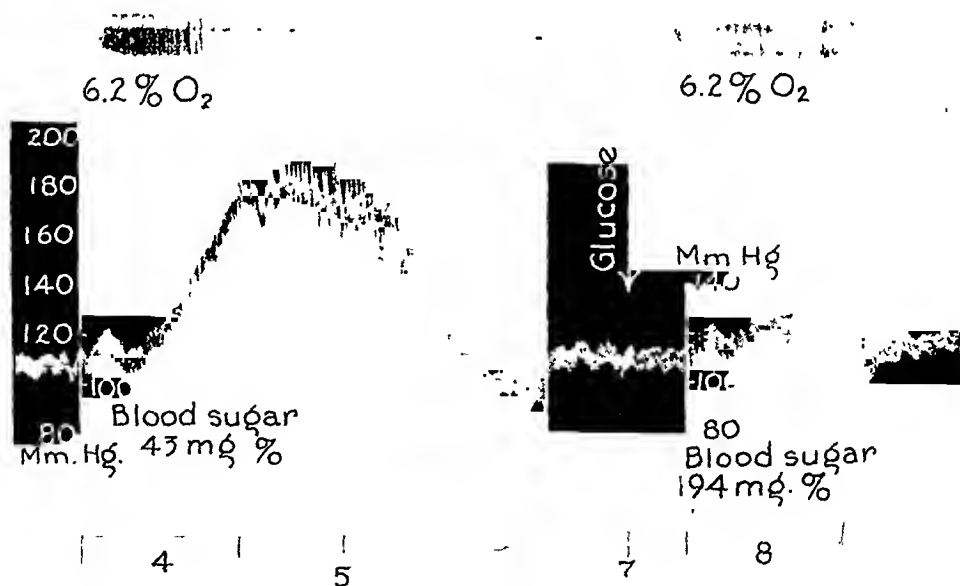


FIG. 1A. In this and the other figures are recorded from above downward: (i) respiration, (ii) blood pressure, (iii) period of 6.2 per cent oxygen inhalation (3 min.). Dog under intraperitoneal sodium amytal anesthesia, 65 mg. per kilo body weight. The amount of insulin injected intravenously varied between 2 and 8 units per kilo. Glucose, levulose, and galactose were injected intravenously either in isotonic or hypertonic solutions. The blood sugar was determined as glucose.



B. Continuation of same experiment, see text.

sumption of the brain, the rate of oxidation in the brain should be diminished to such an extent that a condition prevails comparable to that induced by inhalation of low oxygen tensions. If this were the case, lowering of the blood sugar during a mild degree of oxygen deficiency would induce symptoms of more severe anoxia (as measured in terms of blood pressure response) than would occur at normal blood sugar levels. This would mean, in other words, that as the blood sugar level progressively falls the increment of rise in the blood pressure from inhalation of a given oxygen tension would steadily increase. This indeed has proved to be the case.

#### EXPERIMENTAL METHODS

Dogs anesthetized by intraperitoneal injection of sodium barbital, sodium amytal, or "Chloralosane" were used as experimental subjects. Blood pressures were recorded from the carotid artery by mercury manometer. The femoral artery and vein of one leg were utilized for withdrawal of samples of blood, Lilly's insulin and the various sugar solutions employed were administered by the intravenous route. The dosages of insulin varied from 1.8 units per kilo to 8 units per kilo. Blood sugar determinations were done on protein free filtrates by the methods of Folin and Wu, or by that of Shaffer and Hartman. Determinations of calcium (Kramer and Tisdall), potassium (Kramer and Tisdall), and phosphorus (Kuttner and Lichtenstein, *cf.*, Peters and Van Slyke, 1931) were also made. The pH was determined with the quinhydrone electrode. The dogs were caused to breathe 6.2 per cent oxygen mixed with nitrogen from Douglas bags for 1-3 minutes. This concentration produces, in ordinary circumstances, either no rise in blood pressure or a slight rise. In some experiments pneumothorax was induced and artificial respiration instituted. More than 60 experiments were performed.

## II. RESULTS

### 1. *Augmentation of blood pressure response to oxygen deficiency during hypoglycemia, and its diminution by glucose*

Figures 1A and B show the alteration in the blood pressure response to the inhalation of 6.2 per cent oxygen as the level of the blood sugar is diminished. It is seen that the blood pressure response to 6.2 per cent oxygen is very slight and practically identical when the blood sugar is 110 and 100 mg. per cent respectively. When insulin becomes effective and tests are made with blood sugar at 54 and at 43 mg. per cent enormous elevations of the blood pressure occur (Figs. 1A and 1B). In the latter experiment the change in pressure is so great that distinct vagal pulses develop; the rise in blood pressure, moreover, continues over a considerable period after air had been readmitted. Even in such circumstances the reaction is completely reversible, as the last tracing in Fig. 1B indicates. The intravenous injection of glucose, by which the blood sugar was raised to 194 mg. per cent, restores the original slight response to 6.2 per cent oxygen. A further increase in blood sugar above the normal level, even up to 400 or 500 mg. per cent, did not alter the blood pressure reaction to 6.2 per cent oxygen.

### 2. *The reversal of the blood pressure response to low oxygen tensions in hypoglycemia by different monosaccharides*

Investigations of the relative abilities of the various sugars to combat the hypoglycemic state (Herring, Irving and MacLeod, 1924; Noble and

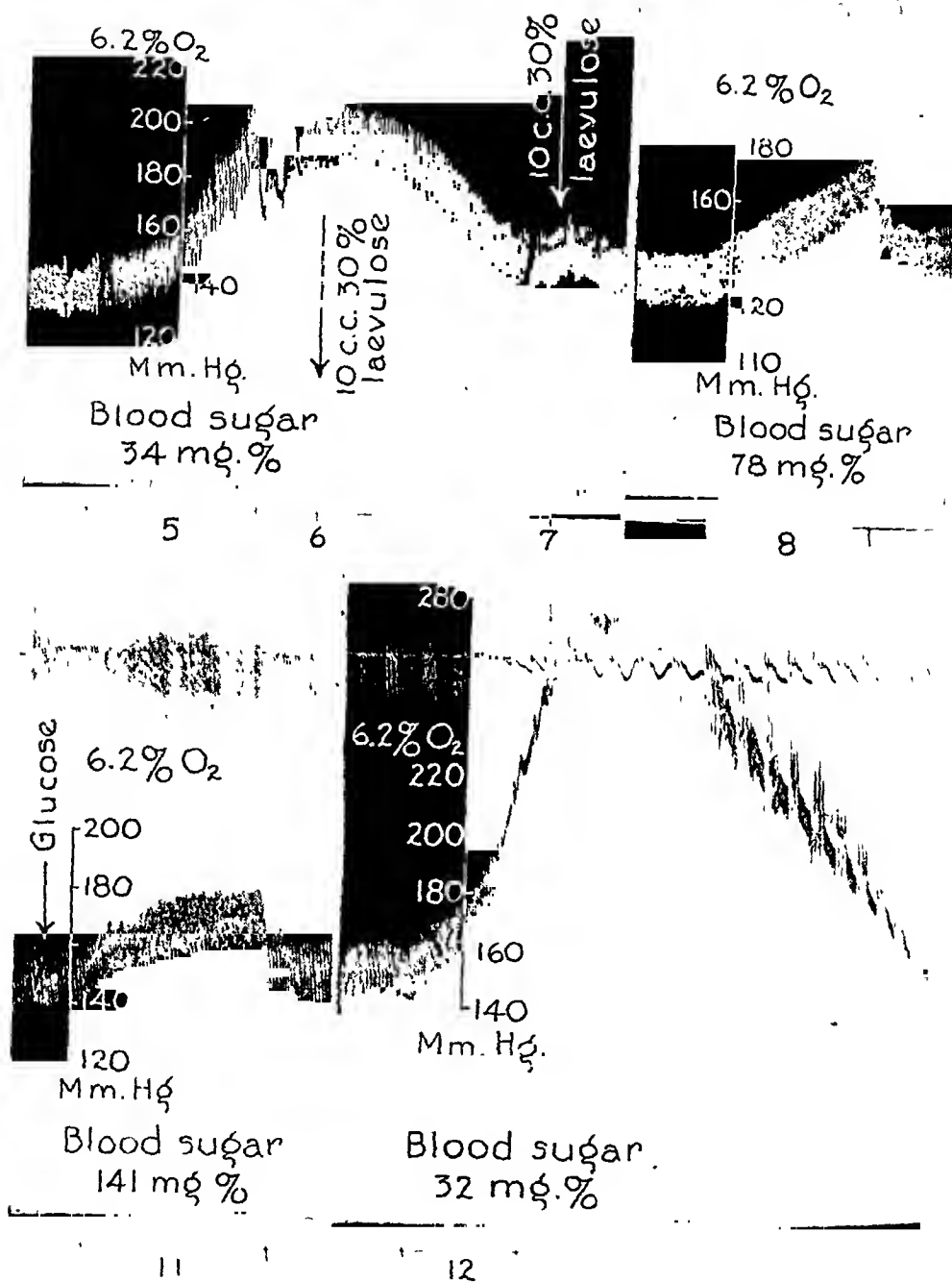


FIG. 2. See text and legend to Fig. 1.

MacLeod, 1923) have shown glucose to be by far the most efficacious. Fructose has a temporary effect and galactose is exceedingly evanescent in its action and then only in mild hypoglycemia. These findings, together with the fact that the blood pressure response to 6.2 per cent oxygen offers a definite insight into the metabolic activities of the brain, led to experiments in which not only glucose, but galactose and fructose were used in attempting to reverse the augmented blood pressure response to oxygen deficiency during hypoglycemia.

Figure 2 indicates that *levulose* has some effect on the blood pressure reaction to inhalation of 6.2 per cent oxygen, since a rise in blood sugar by levulose to 78 mg. per cent (determined as glucose), somewhat lowers the blood pressure response to 6.2 per cent oxygen. Added reduction occurred when a further elevation of the blood sugar level was brought about by injection of glucose. Figure 2 also shows that, even after the sugar had been raised to 141 mg. per cent and a reaction obtained similar to that at normal blood sugar level, the blood sugar began to fall again to 32 mg. per cent causing the blood pressure response to become enormously increased. Since the blood sugar concentration at No. 5 and No. 12 of Fig. 2 were practically identical (34 and 32 mg. per cent respectively) the much greater response at No. 12 indicates that the duration of hypoglycemia is, in addition to the degree of hypoglycemia, an important factor in determining the extent of the blood pressure response.

In general it was found that when the blood sugar was raised to 100 mg. per cent or above by the injection of *levulose* the blood pressure reaction to 6.2 per cent oxygen was not reduced as quickly and as effectively as in similar circumstances when glucose was injected. In some cases, however (cf., the second experiment in Table I), a complete restoration of the original reaction was brought about by levulose.

*Galactose* was also tested in a number of experiments and was invariably found to be ineffective. In Figs. 3 and 4 typical records are given. In each of these experiments a restoration of the original reaction could be obtained by injection of glucose.

### 3. Observations on respiration

During the experiments described above it was frequently observed that after the period of inhalation of 6.2 per cent oxygen Cheyne-Stokes breathing occurred. Such periodic breathing, however, was generally absent as long as the blood sugar was high. If, however, the blood sugar fell below a critical level, which was ordinarily around 40 mg. per cent, Cheyne-Stokes breathing occurred immediately after the inhalation of 6.2 per cent oxygen and readmission of air. Figure 2 well illustrates this phenomenon, particularly at No. 12 where a prolonged interval of periodic breathing occurs at a blood sugar level of 32 mg. per cent, but even at that level the breathing was perfectly regular before 6.2 per cent oxygen was inhaled. In the same experiment a slight indication of periodic breathing was observed in Fig. 2 at No. 5, but this was

Table I. Ability of Fructose to Reverse the Hypoglycemic Blood Pressure Response to 6.2 Per Cent Oxygen.

Time	Blood sugar mgm. %	Blood pressure in mm. of Hg.		Difference in mm.	Remarks
		Before 6.2% O <sub>2</sub>	Max. rise during 6.2% O <sub>2</sub>		
11:15 A.M.	90	121	148	27	15 kilo dog injected* with 60 mg./kilo of amytal at 9:00 A.M. Insulin (120 units) injected intravenously at 10:35 A.M.  Fructose (15 cc. of 30%) injected at 12:15 P.M.
12:10 P.M.	43.7	110	148	38	
12:23 P.M.	104	106	124	18	
12:51 P.M.	42	122	160	38	
11:36 A.M.	72	98	120	22	Another experiment: 16.6 kilo dog injected with 65 mg./kilo amytal at 9:00 A.M. Insulin 8 units/kg. injected between 10:55 and 11:03.  15 cc. fructose injected between 12:18 and 12:21 P.M.
11:57 A.M.	48	101	151	49	
12:26 P.M.	102	110	147	37	
12:43 P.M.	64	102	149	47	
11:12 A.M.	90	122	148	26	Another experiment: 15.0 kilo dog injected with 65 mg./kilo amytal at 9:00 A.M. Chest opened; artificial respiration. Insulin 8 units/kg. injected between 10:30 and 10:35 A.M.  15 cc. fructose injected at 12:15 P.M.
12:07 P.M.	43.7	109	149	40	
12:23 P.M.	104	102	123	21	
1:00 P.M.	42	122	160	38	

\* An injection intravenous; anesthesia sodium amytal in all three experiments.

eliminated by the injection of levulose and glucose. A pertinent illustration is also found in Fig. 3, where marked periodic breathing occurred at 44 mg. per cent blood sugar level after the inhalation of 6 per cent oxygen. It is interesting that the injection of galactose which did not alter the blood pressure response to 6.2 per cent oxygen decidedly improved respiration and diminished the period during which periodic breathing was observed (Fig. 3, No. 7).

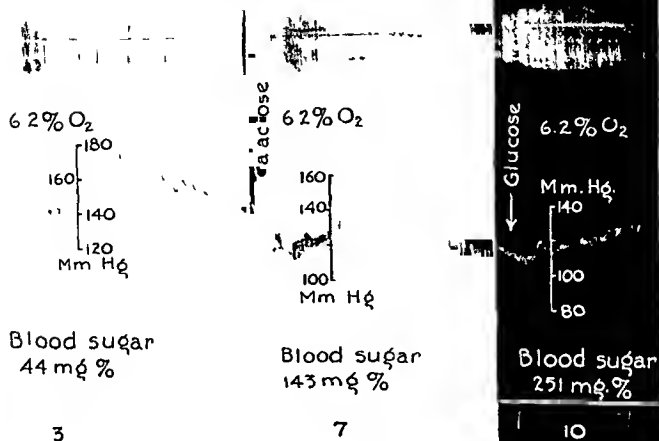


FIG. 3 See text and legend to Fig. 2.

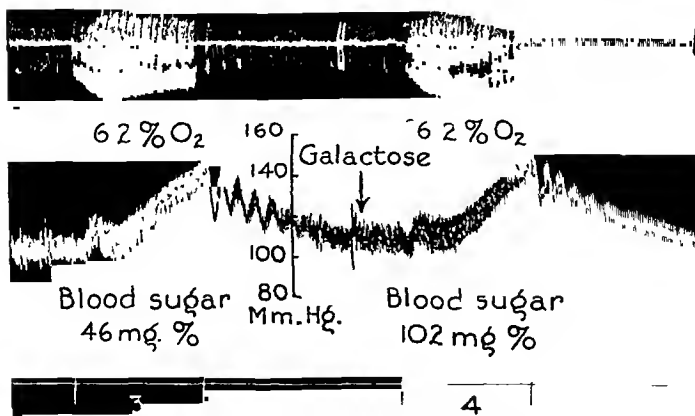


FIG. 4. A further observation on the effects of galactose; see text and legend to Fig. 1.



A further improvement was obtained on injection of glucose (Fig. 3, No. 10). Occasionally it was found that 6.2 per cent oxygen induced a prolonged period of apnea when inhaled at a low blood sugar level. In one experiment the period of apnea lasted for 9 minutes, although before and after this experiment when the blood sugar was higher the respiration was normal. During this long period of apnea it was necessary to resort to artificial respiration to maintain life.

#### 4. Ionic changes in the blood during insulin hypoglycemia

The studies described in this paper have included also an investigation of the concentration of those ions in the blood which influence the excitability of the nervous system. The 9 experiments in which such chemical analyses were made are summarized in Table II. The results indicate great variability in the changes of calcium and potassium, these occurring independently of

Table II. Changes in Blood Chemistry after Insulin.

Insulin units per kg.	K mg. %		Ca mg. %		K/Ca ratio		P mg. %		pH	
	(1)*	(2)**	(1)*	(2)**	(1)*	(2)**	(1)*	(2)**	(1)*	(2)**
1.8	14.4	12.36	13.22	13.25	1.08	0.90	3.4	1.8	7.44	7.27
6.6†	15.6	12.86	12.5	13.34	1.25	0.96	4.1	1.2	7.26	7.39
1.8	26	12.6	11.86	13.0	2.36	0.97	6.8	1.9	7.3	7.33
5.9†	18.6	12.4	14.12	12.92	1.31	0.96	4.3	2.2	7.09	7.09
8	10.11	18.34	12.64	7.54	.80	1.06	4.5	1.6	—	—
6.5	11.16	10.46	7.18	6.14	1.55	1.75	4.4	2.3	7.28	7.25
4.2†	12.25	15.69	7.98	5.17	1.53	3.06	3.2	1.6	7.16	7.24
6.7	21.41	11.02	10.86	12.58	1.97	0.97	4.2	2.2	7.26	7.21
7.2	11.10	13.97	6.49	3.94	1.71	3.50	7.6	3.6	7.31	7.29

\* Before injection of insulin.

\*\* At lowest blood sugar level after insulin.

† Given in two doses separated by brief interval.

both the alterations in the blood pressure and the blood sugar. Phosphorus, however, showed a constant tendency to decrease during hypoglycemia. Such ionic changes are probably of no significance in connection with the phenomena studied. This is obvious with respect to the K/Ca ratio which varies in a random fashion. Although the blood phosphorus decreases regularly with decreasing blood sugar, the rate of decrease of these two substances is quite different, and the augmented blood pressure response to oxygen deficiency is greatest at the lowest blood sugar level, but not at the lowest phosphorus concentration.

As Table II shows, the changes in pH were insignificant except in the first two experiments in which the change was greater than 0.1. While in both experiments the blood pressure reaction increased with falling blood sugar, the pH increased somewhat in one case and decreased in the other. It is improbable therefore that changes in the acidity of the blood play an important part in the reactions just described.

## III. DISCUSSION

The uniformity of the results indicate that with progressive hypoglycemia the blood pressure response to low oxygen-nitrogen mixtures progressively increases. This effect is attributed solely to the changes in blood sugar level and to the duration of the hypoglycemic state. The first contention is proved by numerous experiments in which it was found that: (i) The increase in response corresponds to the blood sugar level and not to the amount of insulin injected. (ii) The increase in blood pressure response to low oxygen is largely independent of other chemical changes which may occur in the blood. (iii) The normal blood pressure response is restored by injection of glucose.

The second contention is based on the fact that the blood pressure response to 6.2 per cent oxygen increases when a given low blood sugar concentration is maintained for some time. With regard to the effect of the various sugars, it is interesting to state that the effectiveness follows the series: glucose > levulose > galactose, which is identical with that found by MacLeod and collaborators (1923, 1924) when they studied the curative effects of various sugars in insulin coma. It was noted that galactose improves respiration although it fails to lower the blood pressure response to the inhalation of oxygen deficient gas mixtures. Since it is unlikely that the excitability of two medullary centers such as the respiratory and the vasomotor center react differently to galactose the findings may indicate a different locus of action in the two cases.

Extensive studies by Gellhorn and Lambert (1938) have shown that the blood pressure response to low oxygen tensions is greatly modified by respiration. Experiments were, therefore, carried out to study the blood pressure reaction to 6.2 per cent oxygen at various blood sugar levels in dogs with pneumothorax and artificial respiration. Since the results were similar to those described in this paper the increased blood pressure response to 6.2 per cent oxygen cannot be attributed to alterations in respiration. Moreover, the differences observed are much greater than those which can be obtained by quantitative changes in respiratory volume.

The greatly increased blood pressure response to 6.2 per cent oxygen indicates that hypoglycemia reduces the rate of oxidations in the central nervous system to such an extent that a further reduction by the inhalation of 6.2 per cent oxygen produces a rise in blood pressure somewhat like that found when oxygen in very low concentrations is inhaled. Although this hypothesis has been supported by our investigations the mechanism by which this is achieved is still obscure. Lambert and Gellhorn (1938) have recently shown that the rise in blood pressure following the inhalation of low oxygen tensions is exclusively due to the stimulation of chemoreceptors in the carotid and aortic bodies, *i.e.*, elimination of their end organs by bilateral vagotomy and denervation of the carotid sinus areas, reverses the blood pressure reaction to low oxygen tension. A fall in blood pressure ensues whereas before the denervation, or after restoration of the temporarily blocked vagus fibers, a rise in blood pressure accompanies the inhalation of low oxygen tension. In

the light of these experiments it is probable that the responsiveness of the medullary centers to afferent impulses originating in the chemoreceptors (carotid body and the arch of the aorta) is increased by hypoglycemia. A final decision of these questions will be given in experiments in animals with removal of all "buffer" nerves.

Finally, attention must be called to the principal differences between the effects of pure oxygen deficiency and those produced by the combination of hypoglycemia and inhalation of low oxygen. The blood pressure response to inhalation of 6.2 per cent oxygen at low blood sugar level is much greater than can be obtained by inhalation of a gas containing a much smaller oxygen concentration or even by inhaling pure nitrogen. Several experiments were carried out in which narcotized dogs inhaled 6, 5, 4, 3, and 2 per cent oxygen, and also pure nitrogen for 1-3 minutes. It was found that those oxygen concentrations which could be inhaled for 3 minutes without causing respiratory and circulatory failure (*i.e.*, 3 per cent oxygen or higher) never caused a rise in blood pressure comparable to that obtained on inhalation of 6.2 per cent oxygen in hypoglycemia. If the oxygen concentration is too low (3 per cent or less) heart failure develops rapidly and the blood pressure falls.

This fundamental difference in the effects of hypoglycemia combined with the inhalation of a moderately reduced oxygen concentration, and of nitrogen inhalation at a normal blood sugar level, becomes understandable if we take into account the fact that hypoglycemia reduces the oxidation rate more in the central nervous system than in other organs of the body. The central nervous system consumes carbohydrates almost exclusively. Its respiratory quotient approaches unity (Lennox, 1931; Dickens and Simer, 1931; Himwich and Nahum, 1932). The heart, however, is able to do work with much lower respiratory quotients. The combination of hypoglycemia with inhalation of low oxygen gas mixtures seems to diminish the oxidative processes in the central nervous system more than any other known procedure without causing death by heart failures. The greatly increased blood pressure response may be taken as an indication of the tremendous excitation of the sympathetic centers. The significance of these findings for the schizophrenia problem is discussed elsewhere (Gellhorn, 1938).

#### IV. SUMMARY

The relation between hypoglycemia and anoxia, as far as the central nervous system is concerned, has been tested by investigating the blood pressure reaction in dogs to a given degree of anoxia obtained by inhalation of 6.2 per cent oxygen. It is known that increasing degrees of anoxia produce proportionately greater rises in blood pressure. On this basis the blood pressure reaction to a given oxygen concentration (6.2 per cent) may be used as an indicator of the degree of oxygen want in the central nervous system. The experiments have shown:

1. Insulin, by virtue of the hypoglycemia produced, causes augmentation in the blood pressure rise to a given degree of oxygen deficiency.

2. This effect is a function of the decrease in the level of blood sugar. This is indicated by: (a) The failure of this augmentation effect to appear in those experiments where insulin did not significantly alter the blood sugar level. (b) The observation that the blood pressure response to the inhalation of 6.2 per cent oxygen varied inversely as the blood sugar concentration. (c) The fact that the restoration of the blood sugar level after hypoglycemia, by the intravenous injection of glucose, diminishes the blood pressure response and restores it to normality.

3. Of the other monosaccharides: fructose, although to a lesser degree than glucose, is capable of lessening the degree of blood pressure response to oxygen deficiency; galactose fails to bring about such reversal.

4. The ionic changes in the blood (K, Ca, H) appear to bear no relation to the phenomenon. The K/Ca quotient shows random variations. The phosphorus concentration decreases with falling blood sugar. The rate of change is, however, different for phosphorus and for blood sugar. The blood pressure response is dependent on the change in blood sugar rather than the change in blood phosphorus.

5. That the oxidative processes in the brain are diminished in hypoglycemia is further indicated by the fact that inhalation of 6.2 per cent oxygen may induce Cheyne-Stokes breathing when the blood sugar is low, although it fails to do so when the blood sugar level is restored by injection of glucose, levulose, or galactose.

6. The increased blood pressure response to oxygen deficient gas mixtures (6.2 per cent oxygen) observed in hypoglycemia is greater than the blood pressure rise obtained on inhalation of pure nitrogen at normal blood sugar levels. This is due to the fact that hypoglycemia, in contrast with the effects of nitrogen inhalation, reduces the rate of oxidation in the brain more than in other tissues. Therefore, a greater reduction in the oxidative metabolism can be achieved and maintained in the brain by combination of the hypoglycemic state with the inhalation of 6 per cent oxygen than by inhalation of nitrogen. In the latter case heart failure develops rapidly and the blood pressure falls.

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# THE DISTRIBUTION OF THE ALPHA RHYTHM OVER THE CEREBRAL CORTEX OF NORMAL MAN\*

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THE MOST characteristic spontaneous electrical activity of the human cerebral cortex is a 10 per sec. oscillation ( $\alpha$  rhythm), yet its origin and distribution over the cortex is still undecided. Adrian and Matthews<sup>1</sup> and Adrian and Yamagiwa<sup>2</sup> reported evidence for the origin of the  $\alpha$  rhythm in the occipital lobes. This view was supported by observations of Tönnies.<sup>2b</sup> On the other hand, Berger<sup>6,7,8</sup> maintained that  $\alpha$  rhythm could arise in parts of the cortex other than the occipital lobes. In agreement with Berger, Foerster and Altenburger<sup>11</sup> found a well defined 10 per sec. rhythm over many regions of the cortex, and Jasper and Andrews<sup>14</sup> concluded that the precentral  $\alpha$  rhythm is independent of the occipital lobes for its origin.

Preliminary experiments revealed that the two opposing interpretations could be substantiated *depending on the method of recording* employed. The present investigation is primarily concerned with (a) the determination of which method of recording electro-encephalograms from electrodes on the scalp gives the truer representation of the  $\alpha$  activity of the brain tissue under the electrodes, and (b) the bilateral distribution of the  $\alpha$  rhythm over the cerebral cortex.

## APPARATUS AND PROCEDURE

Two independent, well-matched amplifiers and ink-writing undulators built by Mr. A. M. Grass were used in conjunction with two filter systems tuned to 10 cycles per sec. The amplification was kept constant throughout the experiments, a 5 mm. pen excursion corresponding to 50 microvolts.

The electrodes were flattened pellets of lead solder, about 2 mm. in diameter, fixed to the scalp with collodion. Electrical contact was made with Sanborn electrode paste. We shall use the term "monopolar" to indicate recording between one lead over active cortical tissue and an earthed (reference) lead on some indifferent tissue (*i.e.*, the mastoid processes). The term "bipolar" will indicate potential changes between two active leads over cortical tissue which are recorded with balanced (push-pull) input amplifiers.

The subject, with his eyes closed, reclined on a bed in a semi-darkened, quiet, shielded room. In the majority of the experiments, performed on 17 adult males, the electrodes were arranged in two rows from the back to the front of the head over both cerebral hemispheres about 3 cm. to either side of the midline. Usually 7 electrodes were fixed to the scalp on each side and potentials from the corresponding leads on both sides were recorded simultaneously. Records were obtained from each subject on at least two different days, sometimes being repeated one or more times on the same day. Fig. 1 illustrates the customary placement of active leads along the head. The electrodes were always placed roughly over the same regions of the cortex by the use of Krönecker's method of cranio-cerebral topography so that differences in size of individual heads were corrected for (Fig. 1).

At least 3 consecutive  $\alpha$  waves with amplitudes of 7 microvolts or more were arbitrarily required to constitute an  $\alpha$  rhythm. (This criterion was first suggested by Dr. Hallowell Davis and Pauline A. Davis in a personal communication.) The percentage of

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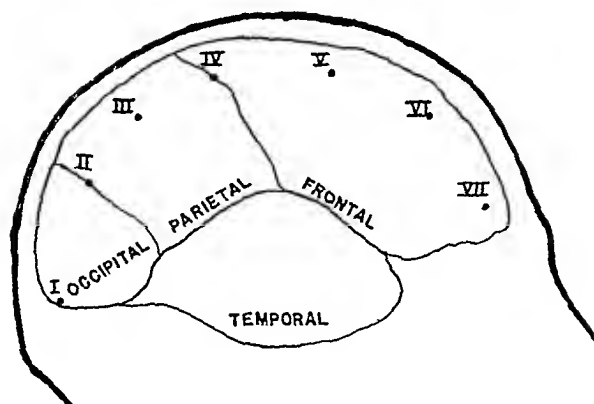


FIG. 1. Diagrammatic representation of one hemisphere of the cerebral cortex illustrating the placement of active leads over it. Roughly, electrode I is over the posterior tip of the occipital lobe; II, over the occipito-parietal fissure; III, mid-parietal; IV, central fissure (fissure of Rolando); V, VI, and VII divide the frontal lobe into 3 approximately equal parts. Usually an equal number of electrodes were similarly placed over the other hemisphere. The distances between successive electrodes were not exactly equal, but about 5 cm. apart for most individuals.

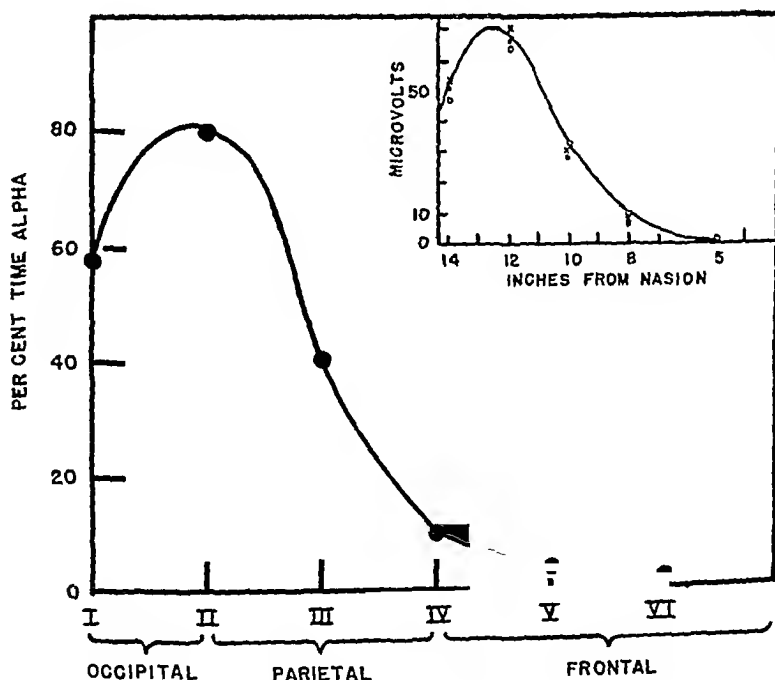


FIG. 2. Distribution of *per cent time alpha* over the right cerebral hemisphere of J. D. (Bipolar Recording). Note the similarity of this curve to the one in the insert (from Adrian and Yamagiwa, *Brain*, 1935, 58: p. 339, Fig. 21B). The distance between the electrodes is almost the same in both curves.

2 consecutive meters of record occupied by the  $\alpha$  rhythm (*per cent time alpha*) was used as the measure of the amount of  $\alpha$  activity in the various cortical areas. (The speed of the moving paper tape was 30 mm./sec. Therefore, it took slightly more than a minute to obtain 2 meters of record.)

### RESULTS

When electro-encephalograms were recorded between successive pairs of active leads (bipolar) separated by about 5 cm., the *per cent time alpha* was distributed over the cortex\* in a manner similar to that found by Adrian and Yamagiwa<sup>2</sup> for the average amplitude of the  $\alpha$  waves (Fig. 2). The close

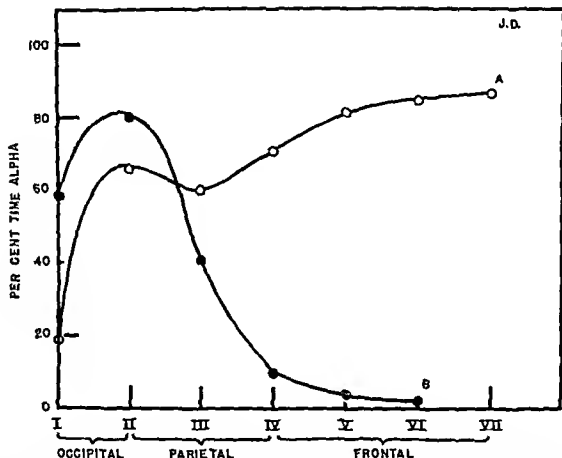


FIG. 3. Distribution of *per cent time alpha* over the right cerebral hemisphere in J. D. with monopolar recording (Curve A, open circles) and with bipolar recording (Curve B, solid circles). The data for the two curves were taken simultaneously and therefore are strictly comparable.

similarity between the two curves bears out the direct relationship often observed between the *per cent time alpha* and the amplitude of the  $\alpha$  waves making up the rhythm. Furthermore, Fig. 2 illustrates the ease with which Adrian and Yamagiwa's results may be reproduced, and is in harmony with an occipital origin of the  $\alpha$  rhythm. They also used bipolar recording in their experiments. However, when records were obtained from the same electrodes and the same subject as in Fig. 2 using monopolar instead of bipolar leads,

\* We cannot insist on the precise shape of the individual parts of the curve in Fig. 2 or in any of the other figures in this paper, since the points on the curves are about 5 cm. apart. We can say, however, that it is legitimate to draw smooth curves between the points since our results from closely spaced (1 cm. apart) electrodes indicate that the points of inflection are not sudden or very sharp.



the *per cent time alpha* was found to be distributed in a different way. The curve (A) connecting the open circles in Fig. 3 represents the distribution of *per cent time alpha* with monopolar recording. The solid circles curve (B) is the same as that in Fig. 2.

The two curves are much alike for the occipital and the first part of the parietal areas (Fig. 3). The *per cent time alpha* distribution over the frontal cortex, however, differs markedly with the two methods of recording. Curve A supports the generalized origin of the  $\alpha$  rhythm, claimed by Berger, since a higher *per cent time alpha* in the frontal lobe could not possibly be due merely to spread of the rhythm from the occipital lobe. The amplitude of the  $\alpha$  waves throughout most of the frontal lobe was appreciably greater than in the occiput. The type of distribution curve obtained must depend on which of the two recording techniques is employed. Accordingly, a series of control experiments was devised to obtain a better understanding of these methods.

#### MONOPOLAR (GRID-GROUND) RECORDING

(1) *Is the grounded (reference) lead truly an "indifferent" lead?* The *per cent time alpha* from any region of the cortex was the same whether the mastoid processes or the ear lobes were used for reference points. When active electrodes were placed on each of the mastoid processes, the ears serving as reference tissue, no appreciable *per cent time alpha* was observed. The same was true when the earthed lead was placed on the bridge of the nose. Bipolar recording between the two mastoid processes gave essentially the same results, which were independent of the absolute value of the occipital *per cent time alpha*. We believe, therefore, that electrodes placed on the mastoid processes, on the ear lobes, or on the bridge of the nose constitute satisfactory reference leads.

(2) *Distance between electrodes.* Records were taken from the same grid electrode on the scalp, using the nose and mastoid electrodes simultaneously as reference leads. The *per cent time alpha* from the various electrode positions along the head was always the same for both reference and given active electrode combinations (in fact, the two records were superimposable), although the distance from nose to the active electrode and from mastoids to the same active lead was never equal.

We conclude that with monopolar recording the *per cent time alpha* obtained is a measure of the amount of activity under the active electrode, and that neither the reference lead nor the distance between it and the active electrode contributes materially to the picture.

#### BIPOLAR (PUSH-PULL) RECORDING

The distance between active leads in bipolar recording undoubtedly plays a rôle in determining the "net" potential changes recorded between the leads. It is, however, by no means the most important factor. The different *per cent time alphas* (see Fig. 3, A and B) obtained with the monopolar and bipolar methods may result from factors operating singly or, more probably, in un-

predictable combinations in the latter method. From the magnitude of the *per cent time alpha*, phase relations, synchronization of  $\alpha$  "bursts" of activity and "silent" periods, and amplitude of the  $\alpha$  waves occurring under both electrodes simultaneously determine to what degree the true  $\alpha$  activity which exists under each electrode may be distorted by bipolar recording. The way in which these variables may act is illustrated by the following experiment.

Five electrodes were placed at intervals of 1 cm between our standard electrodes II and III (occipito parietal fissure to mid-parietal region). This region was chosen since approximately the same distribution curve is obtained here with both monopolar and bipolar recording, and because marked phase shifts occur in this region (Adrian and Yamagiwa<sup>2</sup>). Records were obtained from the various bipolar combinations simultaneously with monopolar arrangement of the same active electrodes, so that the *per cent time alphas* in

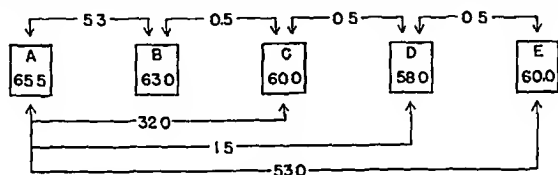


FIG 4 Electrodes A, B, C, D, and E placed at intervals of about 1 cm between the occipito parietal fissure to the mid parietal region. Lead A corresponds to our standard lead II (occipito parietal fissure) and electrode E to standard lead III (mid parietal). Figures within the squares represent the monopolar *per cent time alpha* for each electrode placement. All other figures represent *per cent time alphas* obtained from combinations of the same electrodes using bipolar recording. Subject J. D. Compare these monopolar values with those between leads II and III in Fig. 3.

Fig. 4 are comparable. Bipolar leads give markedly different *per cent time alphas* from monopolar leads, and they do not bear any constant relationship to the latter. The monopolar *per cent time alphas* for electrodes A, D, and E were about the same, namely, approximately 60.0. Bipolar *per cent time alpha* between A and D, however, was 1.5, and that for A to E 53.0. Recording between bipolar leads spaced farther and farther apart along the head (I-II, I-III, I-V, etc.) and between analogous leads on each hemisphere (II left—II right) gave similar anomalous results. Obviously, we are not dealing simply with an algebraic difference between the amounts of  $\alpha$  activity under the two electrodes.

We have obtained bipolar *per cent time alphas* which were much higher than that under each electrode alone. In such cases, even when the grid ground *per cent time alphas* under each electrode were identical, the bursts of  $\alpha$  activity did not occur simultaneously under both electrodes, but, in the main, first under one and then under the other. The net effect of this situation was an almost continuous  $\alpha$  rhythm for certain stretches of record and much less activity in other portions of the record where more synchrony of  $\alpha$  bursts

occurred under the electrodes. On the other hand, even when the bursts of activity occur simultaneously under both electrodes, the amplitude of the  $\alpha$  waves in the bipolar tracing may be considerably lower than in either of the monopolar tracings. Further complications in bipolar recording would also arise when the individual  $\alpha$  waves under both electrodes are not in phase.

### THE BILATERAL DISTRIBUTION OF PER CENT TIME ALPHA

(1) *Foci of maxima.* It was unusual for both hemispheres to show the same distribution of *per cent time alpha*. A typical set of curves is shown in Fig. 5. There usually was at least one other region of maximal  $\alpha$  activity be-

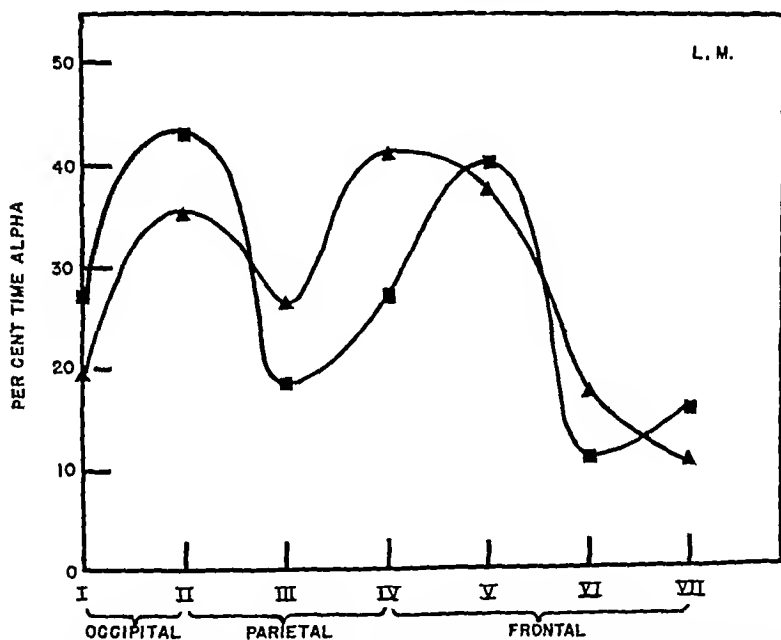


FIG. 5. Distribution curves of *per cent time alpha* for the left (solid squares) and the right (solid triangles) cerebral hemispheres of L. M. with monopolar recording, illustrating differences in magnitude and foci of maxima of *per cent time alpha* in the two hemispheres.

sides the occipital lobes. This other region was not always in the same portion of the frontal lobe in each hemisphere. For example, in Fig. 5 the left frontal lobe maximum was under lead V, whereas on the right side it was under electrode IV.\* The curves from leads I to III, however, were usually the same for both hemispheres, differing only in absolute values.

(2) *Variability.* The frontal distribution curves varied a great deal from individual to individual (compare Figs. 3A and 5). For a given subject it may vary within comparatively short periods of time or from day to day. These statements apply to the majority of the 17 subjects studied, although we

\* The distance from IV to V (about 5.0 cm.) is too great to explain the difference in foci of maxima in the frontal lobes on the basis of an anatomical asymmetry of the two hemispheres.

have seen some individuals whose distribution of *per cent time alpha* was relatively constant. Fig. 6 illustrates the fluctuation of the distribution curves of subject O.S. for the right cerebral hemisphere only. Curve B was obtained from the same electrodes as Curve A, but one half-hour later. Curve C was obtained from the same individual one day later.

The first portions of all 3 curves are quite similar. Although the magnitude of *per cent time alpha* may vary within the limits of variability for a

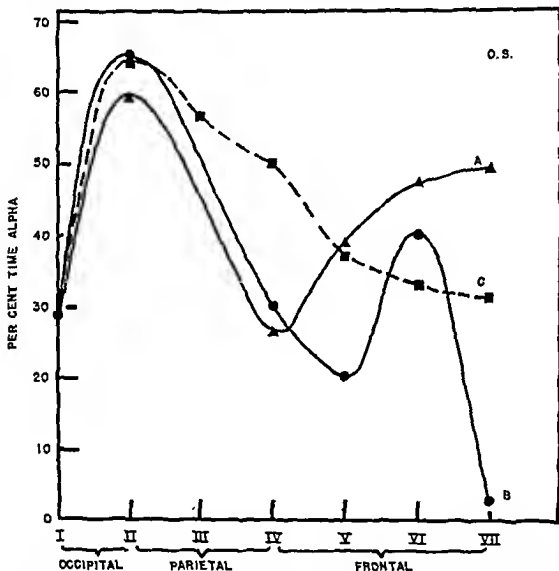


FIG. 6. The distribution of *per cent time alpha* over the right cerebral hemisphere of O.S. obtained with monopolar leads. B, taken  $\frac{1}{2}$  hour after A; C, one day later.

given individual, the shape of the distribution curve for leads I-IV is extremely constant. In general, this portion of the curve is the same from person to person irrespective of absolute *per cent time alpha* values.

The extreme variability of the frontal *per cent time alpha* may be the source of another complication in bipolar recording, since the relationship between successive pairs of electrodes changes so radically and frequently. For example, one subject who had a very low occipital *per cent time alpha* showed almost no  $\alpha$  activity over the left frontal lobe on one day. On another day much more  $\alpha$  activity was found under lead VII than under lead II.

(3) *Synchrony of bursts of  $\alpha$  activity in the two hemispheres.* The bursts of

$\alpha$  waves from the two cerebral hemispheres seldom occurred simultaneously in the occipital lobes,\* especially in individuals with low or medium *per cent time alphas*. As one progressed anteriorly along the head, synchronization of the bursts of  $\alpha$  activity from the two hemispheres became much greater in most cases, until finally almost perfect unison was present in the anterior portion of the frontal lobes. However, this was not true for all the subjects, especially those with very high *per cent time alphas*. Berger<sup>6,8</sup> had previously reported somewhat similar differences between the two hemispheres and considered them as evidence in favor of the view that regions other than the occipital lobes could produce the  $\alpha$  rhythm. Furthermore, bursts of  $\alpha$  activity and the "silent" periods between them were seldom synchronized in the various regions of a hemisphere. In view of these facts, one may infer that the  $\alpha$  rhythms in both hemispheres are relatively independent of each other,† and that the  $\alpha$  rhythm may originate in any of the various regions of a hemisphere.

(4) *Alpha frequency*. It was often found that the frequency of the  $\alpha$  waves in the frontal lobes was slower by one or two cycles than that in the occiput. The objection might be raised that we are not dealing with the same rhythm in the back and in the front of the head. This frequency difference was not found in all individuals, and regardless of whether the frequency was the same or not, the frontal rhythm was just as completely obliterated on opening the eyes as was that of the occiput. This would argue against any specificity of the  $\alpha$  rhythm for visual functioning. The  $\alpha$  rhythm seems to be an electrical activity common to all parts of the cerebral cortex, and it can be produced everywhere in the cortex.

### DISCUSSION

It is apparent that bipolar recording is not satisfactory for determining the amount of  $\alpha$  activity from the cerebral cortex. Only the occipital and part of the parietal lobes give similar results with both methods of recording. "Standard" placements of bipolar electrodes over various regions of the frontal cortex, therefore, do not seem feasible. We consider monopolar recording superior to the bipolar method only for determining the amount of  $\alpha$  activity (*per cent time alpha*), recognizing that bipolar recording may offer special advantages when employed for investigating other aspects of the electroencephalogram.

The evidence of Adrian and Yamagiwa<sup>2</sup> on phase change studies along the head favored the occipital origin of the  $\alpha$  rhythm. Jasper and Andrews<sup>14</sup>

\* Liber<sup>17</sup> has reported ependymal streaks and accessory cavities in the tip of one or both occipital horns (most frequently in the right hemisphere) in 16 out of 50 unselected human brains. He attributed the pathology to occlusion of the occipital horn by the growth of tissues surrounding it. This might be at least partially responsible for the differences in electrical activity which we have observed in the two occipital lobes of many subjects.

† Jasper and Andrews<sup>13</sup> found no constant phase relationship between the  $\alpha$  activities under electrodes over the left and right occipital lobes. They regarded this as evidence of a certain amount of independence of activity between the two occipital fields.

have confirmed their observations in some subjects, but in other subjects the phase changes along the head were not in agreement with Adrian and Yamagiwa's interpretation. We have not studied the temporal  $\alpha$  rhythm, but Laugier and Liberson<sup>16</sup> report that the origin of the temporal rhythm is not the same as that for the occipital rhythm.

The  $\alpha$  rhythm may originate in the occipital cortex and then may be conducted to other regions of the cortex by sub-cortical pathways. If this were true, we should expect to find rather close synchronization between the bursts of  $\alpha$  activity in the occipital lobes and other cortical areas. Actually, this is not the case. Moreover, preliminary investigations (in collaboration with Drs. Hoagland, Cameron, and Tegelberg) on the relationship between hypothalamic and cortical potentials in man show that (a) an  $\alpha$  rhythm is never present in the hypothalamus unless it occurs also in the cortex, and that (b) the *per cent time alpha* is higher in the cortex than in the hypothalamus. This evidence is in favor of the generalized origin of the rhythm over the cortex, and it indicates that the rhythm arises spontaneously from cortical cells independent of other central nervous influence.

We have recently completed a study of the variability of the occipital *per cent time alpha* (Rubin<sup>19</sup>). The variability of the *per cent time alpha* in most of the other cortical areas seems to be appreciably greater than that in the occipital lobes although we have not systematically investigated the former. Judging from the occipital variability, the instability of the frontal *per cent time alpha* is not accountable for in terms of any variability inherent in the processes producing the  $\alpha$  rhythm, but is rather the result of other nervous influences playing upon it.

The greater part of the cerebral cortex receives afferent fibers from the thalamus (Ariëns Kappers, Huber, and Crosby<sup>3</sup>). Since, under our conditions of recording, the subject's eyes are closed, we would not expect the occipital  $\alpha$  rhythm to be affected by afferent impulses relayed to the occipital lobes by the thalamus. In fact, the occipital  $\alpha$  rhythm is just as unstable as the frontal rhythm if the eyes are kept open while electro-encephalograms are being taken. The frontal lobes, however, may be influenced by thalamo-cortical impulses set up by changes in the subject's external and internal environment. The frontal lobes also receive connections from the hypothalamus (Papez<sup>18</sup>). In view of Bard's<sup>4</sup> evidence that the hypothalamus elaborates afferent impulses that reach it, giving them "emotional" content, even slight, transitory "emotional" excitation might well be reflected in the frontal cortex. Recently Grinker<sup>12</sup> has reported that electrical stimulation of the hypothalamus in the cat and in man altered both the autogenous electrical activity of the hypothalamus and that of the cortex. Grinker's observations and the well-known fact that apprehension, embarrassment, etc., usually inhibit the cortical  $\alpha$  rhythm are consistent with the notion that sub-cortical brain levels contribute to the marked fluctuations of the frontal lobe *per cent time alpha*.

The amount of  $\alpha$  activity in the cortex may not be simply a direct result of the activity of lower brain levels. Bartley<sup>6</sup> has shown that the entire cortex

of the dog is involved to varying degrees in response to sensory stimuli; the greatest response occurs in only one or two areas, but other areas are also affected. Blake and Gerard,<sup>9</sup> from their experiments on sleep, have suggested that indirect channels from one cortical region may influence other regions, and that the pre-existing state of the cortical neurons determines their response at any given time. Not only do intracortical pathways probably exist within a hemisphere, but pathways from one hemisphere to the other also have been reported. For example, evidence presented by Kornmüller<sup>15</sup> and by Elsberg and Spotnitz<sup>10</sup> indicates the presence of a crossed pathway which connects one frontal lobe with the occipital lobe of the opposite side.

### SUMMARY AND CONCLUSIONS

Electro-encephalograms were obtained from 17 subjects to determine the distribution of the  $\alpha$  rhythm over the cerebral cortex and to evaluate the use of monopolar and bipolar recording for this purpose. The following results were obtained:

1. Monopolar recording from electrodes on the scalp gives a truer representation of the amount of 10 per sec. activity (*per cent time alpha*) in the cerebral cortex than does bipolar recording.

2. There were at least two regions of the cortex which showed maxima of  $\alpha$  activity—usually some part of the occipital and frontal lobes. The curve describing the occipital lobe distribution of *per cent time alpha* was very stable and could be reproduced, even over long periods of time. The distribution curve for the frontal lobe, however, was extremely variable, fluctuating over short intervals ( $\frac{1}{2}$  hour) and from day to day.

3. The bursts of  $\alpha$  waves from the two cerebral hemispheres of some individuals were least synchronized in the back of the head, more perfect unison between the two rhythms being obtained the further anterior one recorded along the head.

4. The bursts of  $\alpha$  activity and the "silent" periods between them in the occiput did not occur simultaneously with the bursts and "silent" periods in the frontal lobes. Often the frequency of the  $\alpha$  waves in the frontal lobes was found to be slower than that in the occipital lobes; waves of both frequencies, however, were obliterated when the subject opened his eyes.

5. The evidence reported here indicates that the  $\alpha$  rhythms of the two hemispheres are relatively independent of each other, and that the  $\alpha$  rhythm may arise in all regions of the cerebral cortex.

6. Factors which might account for the marked fluctuation of the frontal lobe *per cent time alpha* are discussed.

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# EFFECTS OF BLOOD PRESSURE CHANGES ON CORTICAL POTENTIALS DURING ANESTHESIA

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DURING a study of the effects of anesthetic agents upon the electrical activity of the cerebral cortex it appeared that some of the outstanding differences between the agents might be due to their secondary actions. For example, it has been shown<sup>5</sup> that the pattern of cortical action potentials in cats under ether varies widely from that found when pentobarbital is the anesthetic agent. Deep anesthesia under the latter drug is frequently associated with a low systemic blood pressure. Any attempt to evaluate the differences between such agents requires a consideration of the influence of low blood pressure *per se*. The purpose of this paper is to describe the rather striking cortical effects induced by altering the level of the systemic arterial pressure.

## APPARATUS AND METHOD

*Animals.* Cats were studied under third stage (surgical) anesthesia. The right posterior sigmoid gyrus of the cortex was exposed. Activity was recorded from the region of the sensory area.

*Anesthetic agents.* Ether and pentobarbital sodium were used. Ether was administered through a tracheal cannula. When a high concentration was desired, all the air breathed was drawn over an ether surface. When a lighter degree of anesthesia was indicated, a by-pass for air was opened. Pentobarbital sodium was administered intraperitoneally, using 0.33 mgm. per kgm. Deep anesthesia was obtained by increasing the dose by 50 to 100 per cent. The effects of changes in the blood pressure were studied only when the level of anesthesia had become constant as determined by identical flexion reflexes following sciatic stimulation.

*Blood pressure and its regulation.* The blood pressure was recorded from a glass cannula inserted into the left common carotid artery. The cannula was filled with 5 per cent citrate solution. The blood pressure was regulated in the manner described by Cannon,<sup>4</sup> *i.e.*, through cardiac tamponade. A cannula is tied into the pericardium and Ringer's solution introduced into the pericardial sac; the Ringer's solution flows from a levelling bulb and the intrapericardial pressure is regulated as desired.\* The systemic arterial pressure can thus be abruptly altered and held at any level below the normal, or returned quickly to normal. This method greatly increases the intracranial venous pressure. Lowering of the blood pressure by bleeding (see below) caused a comparable effect on cortical activity. It seems unlikely that the high venous pressure of itself produced any effect. When the blood pressure was lowered by bleeding (one case) it was not possible to restore the pressure quickly to normal. This technic was accordingly not suitable for the experiment.

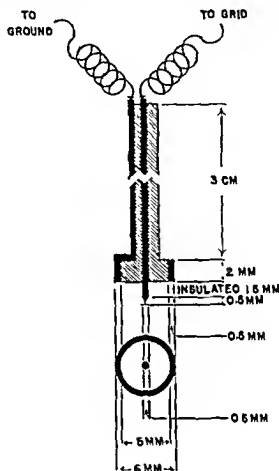
*Sensory stimulation.* The central end of the left sciatic nerve was inserted into tube electrodes which were placed in circuit with stimulating apparatus consisting of a hand

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\* It is customary to use a glass cannula for this procedure. We found, however, that one prepared in the following way was easier to insert. Remove the bevel from the end of an ordinary 18 gauge needle, and then place a drop of solder around the orifice, making a terminal knob. Place another drop of solder 2 mm. above this on the shaft of the needle. Hold the pericardium up with two pairs of blunt forceps; prick a hole in it with a needle and then force the cannula into the sac until both knobs are inside. Tie above each of these, and allow the pericardium to fall back into its natural position. During the time the chest is open oxygenation must be maintained by positive pressure respiration.

operated mercury contact key, a 1.5 volt dry cell, a string galvanometer signal device (Forbes and Cattell<sup>6</sup>), and a Harvard inductorium. The stimuli were make and break shocks spaced from one to three seconds apart, usually followed by a rapid series of shocks (by hand). The homolateral nerves to the hamstring muscles were left intact in order that a flexion response of the lower leg might occur and be recorded on a smoked drum. The activity of this reflex following stimulation was used as one indication of the depth of anesthesia.<sup>5</sup>

*Electrodes.* Various types of electrode were used; first, plates with one plate on the cortex and the other outside the skull; second, "bipolar" surface electrodes having a separation of 1.5 mm. were employed; finally, we used concentric electrodes. These with their



#### CONCENTRIC ELECTRODES

FIG. 1. The concentric electrodes; section and end view.

dimensions and general arrangement are shown diagrammatically in Fig. 1. Potential differences were recorded between the surface of the cortex and the interior. The central electrode which was chosen as the grid lead, was formed as a spike and everywhere insulated except at its tip. The central spike was surrounded by a circular band, the ground lead. The electrodes were of silver supported by a hard rubber base. Fresh silver chloride was deposited upon them electrolytically each time before using.

The pictures obtained with the concentric electrodes do not differ fundamentally from those obtained with the other types. Recording with the concentric electrodes was more satisfactory since pulsation of the cortex from the heart beat and respiration is often troublesome with the bipolar electrodes. With the concentric electrodes disturbance from this cause is minimal, for the flange of the ground lead usually fills the opening in the skull made to identify the desired cortical position. The potential difference appears to be somewhat greater when the leads are taken from below the surface of the brain than from two surface areas. This makes brain varies rather widely in volume at various le

of circulatory changes, and this usually necessitates adjustment of most electrodes. The concentric type described here requires less attention than the others. This type is also strong and durable.

**Amplifier.** The potential changes between the ground and grid leads were amplified by the direct-coupled apparatus described by Forbes and Grass<sup>7</sup> and recorded on film with a Hindle string galvanometer. A timer with 10 msec. units recorded on one margin of the film; a string and magnet were used for recording make, break and series (by hand) stimuli on the opposite margin.

## RESULTS

Notwithstanding wide variations in the "normal" pattern of electrical activity in the cortex, certain constant changes in this activity, such as de-

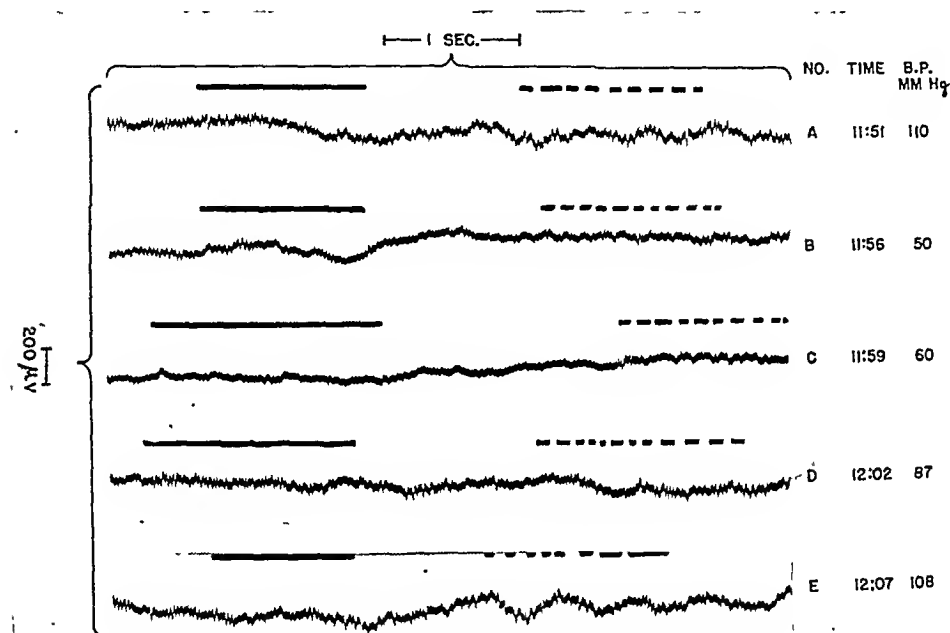


FIG. 2. This shows the effects of low blood pressure upon the cortical potentials under ether anesthesia. Reading from left to right a "make" shock is indicated by the beginning of the broad black band, a "break" by its termination. In this and all subsequent records an upward deflection signifies negativity of the grid electrode; this was always the central electrode which penetrated the cortex.

crease in potential of the waves, are correlated with depression of blood pressure. Other effects, such as the "spike" response,<sup>5</sup> more appropriately designated the secondary discharge (See Fig. 5C) can be elicited at one time but not at another. Probably this effect can be brought out only in a relatively narrow zone. It will be considered in the Discussion.

## Ether

The dominant frequency of the rapid waves under ether is of the order of 40 per sec. (See Fig. 2). The basic frequency is not significantly altered by variations in blood pressure of the extent shown here. Prolonged depression

of the blood pressure will abolish the waves (See Fig. 3). When the concentric electrodes are used and the potential difference between the interior (2 mm. deep) and the surface of the cortex recorded, the largest of the rapid waves show an amplitude of about 60 micro-volts at a normal blood pressure. At a "shock" level (Fig. 2C), this amplitude is reduced by nearly 50 per cent.

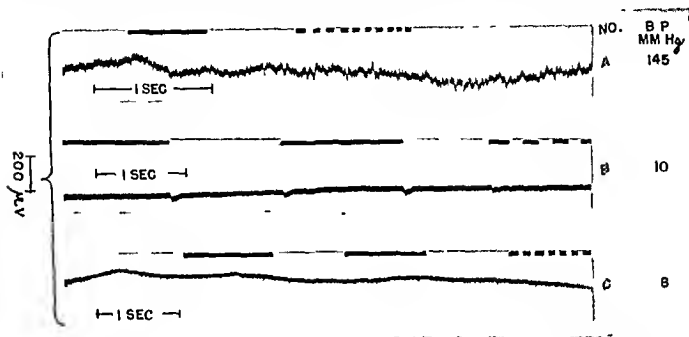


FIG. 3. Ether anesthesia. Blood pressure lowered by hemorrhage. This shows the appearance of the "secondary discharge" following sciatic stimulation, and its disappearance on repeated stimulation.

A true secondary discharge following sciatic stimulation was elicited under ether only when the animal was in poor general condition, following lowering of the blood pressure by hemorrhage (Fig. 3B). The disappearance of the effect following repeated stimuli is characteristic and evident here. This phenomenon occurs with a latency of 40 to 60 msec. It is clearly distinguished

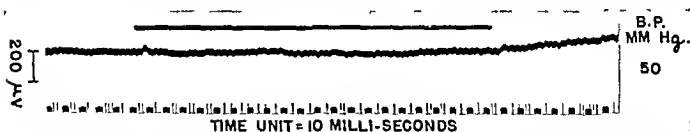


FIG. 4. A record of the arrival in the cerebrum of the afferent volley following sciatic stimulation. Ether anesthesia. Cortical activity depressed by low blood pressure.

from the arrival in the cerebrum of the afferent volley initiated by sciatic stimulation, both by its greater latency and by its absence in the response to all but the first one or two of a rapid series of stimuli.<sup>5</sup> The usual ether pattern is such that the arrival of this volley in the cerebrum cannot be detected; but, when the amplitude of the waves has been greatly depressed by a low blood pressure, the contrast is great enough to demonstrate it as in Fig. 4 (rapid

film). Restoration of the blood pressure to normal is quickly followed by a resumption of activity in the cortex (Fig. 2E).

### *Pentobarbital sodium*

The pattern of activity under light anesthesia with this agent is somewhat similar to that found in unanesthetized cats.<sup>5</sup> The large excursions at normal blood pressure are of the order of 10 per sec. (Fig. 5). Superimposed upon these are smaller, more rapid waves having a frequency of about 25 per sec. The amplitude of the large excursions indicates a potential of as much as 200 microvolts, while the faster waves show a potential of the order of 50

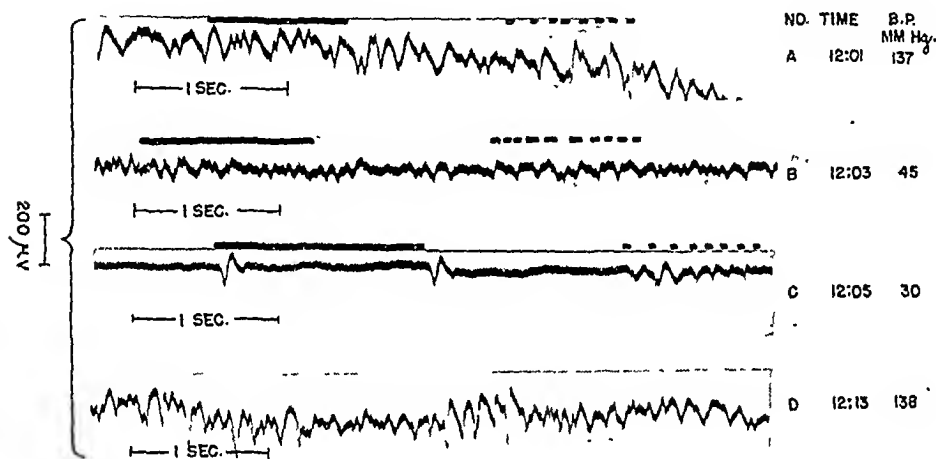


FIG. 5. This shows the various effects on cortical activity of several levels of blood pressure under light pentobarbital anesthesia. The "secondary discharge" has been evoked following sciatic stimulation and is recorded in record C. Its disappearance on repeated stimulation is also shown.

microvolts. Depression of the blood pressure can obliterate all spontaneous waves as in Fig. 6C and D. Restoration of a normal blood pressure is quickly followed by the appearance of the original pattern (Figs. 5D and 6E).

Heretofore the secondary discharge had been elicited only under deep pentobarbital anesthesia, under tribromethanol anesthesia or under asphyxia.<sup>5</sup> We have found in this study even when the anesthesia is light, as indicated by a very active flexion reflex, that it is easy to bring it out merely by lowering the blood pressure and stimulating the sciatic (Fig. 5C). The typical fatigue of the effect following rapid stimuli is also shown here. It appears possible to lower the blood pressure to such an extent that it becomes impossible to elicit the phenomenon, as in Fig. 6D. At the extreme left of this record a suggestion of the effect appears; in the later part it is absent.

### DISCUSSION

Critical reduction of the systemic arterial blood pressure introduces numerous factors for consideration which have not yet been well evaluated in

their cortical effects. Undoubtedly important are the resultant anoxia and the fall in pH of the tissues. A clear understanding of these factors will require much further study. If, at a constant level of anesthesia the blood pressure is suddenly lowered, the flexion reflex produced by stimulation of the sciatic is abruptly depressed, the spontaneous activity in the cerebral cortex is diminished. Further lowering of the blood pressure results in failure of the flexion reflex, and if the pressure is lowered still further the recorded activity in the cortex disappears. These effects are identical with those induced by

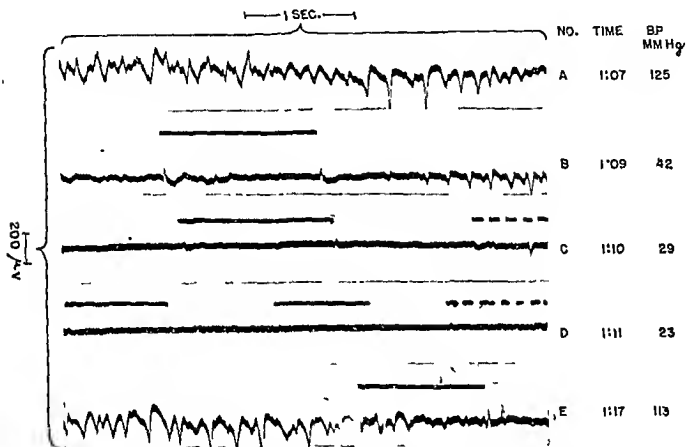


FIG. 6. Pentobarbital anesthesia. In record D the "secondary discharge" fails to appear clearly, following sciatic stimulation.

deepening the anesthesia, and, like the effects of deep anesthesia, can be overcome by reversing the causative process. In other words, simple lowering of the blood pressure results in a reversible depression of cortical activity which is indistinguishable from that occasioned by anesthetic agents; indeed one is forced to conclude that the consequences of lowering the blood pressure, if not identical, are at least similar to those occasioned by increase in depth of anesthesia. The clinical implications of this are obvious and need not be dealt with here.

Derbyshire, Rempel, Forbes and Lambert<sup>6</sup> have described the cortical effects of sciatic stimulation under deep pentobarbital anesthesia and deep tribromethanol anesthesia. A small initial excursion of the base line occurs with a latency of 10 to 12 msec. after sciatic stimulation. This, it is assumed, represents the arrival in the cerebrum of the afferent volley. Under the agents

just described, as well as under asphyxia, this primary deflection is followed by a secondary excursion, with a latency of 30 to 60 msec. It may be either mono- or di-phasic, and is, under certain conditions, reversible.<sup>5</sup> This effect, which we now call the secondary discharge, is obtained when the recorded spontaneous cortical activity has been abolished. The phenomenon quickly fails on repeated stimulation. The effect did not appear under ether unless asphyxia was superimposed upon the anesthetic. They suggest the possibility that pentobarbital and tribromethanol suppress activity in the cortex without blocking the sensory paths leading to it, but that ether blocks these paths before cortical activity is suspended.

Unpublished studies by Forbes and Rempel, in conjunction with those of Adrian<sup>1</sup> and Bishop<sup>2</sup> suggest that this phenomenon may be a cortifugal response following arrival of the afferent impulses in the cortex. Bishop and O'Leary<sup>2</sup> have found a similar effect in the optic nerve. Here they report that a single maximal stimulus applied to the optic nerve in rabbits under light ether anesthesia leads to a response of the optic cortex in which they differentiate four components. The first two are di-phasic potentials. These may be fused into one, of which the first phases involve positivity of the surface of the cortex. The third component is a slow surface-negative deflection, whereas the fourth is a slow surface-positive deflection.

Adrian<sup>1</sup> has found in the rabbit's cortex under di-allyl barbituric acid anesthesia that electrical stimulation of the cerebral cortex causes characteristic changes in surface potentials. Weak shocks make the stimulated region negative to points a few mm. distant, although these stimulated points may still be positive to more distant points. In this case this effect is due to neurones in the superficial layers of the cortex. The form of the response is changed by repeated stimulation with stronger currents. Here the chief potential change is due to elements activated at some distance below the surface. He reports that good oxygenation of the cortex is necessary for the condition in which each wave of activity travels a little further than its predecessor. Under conditions in which the spread of waves is favored the period of stimulation may be followed by after-discharge.

Somewhat puzzling is the appearance, under ether, of the secondary discharge in response to sciatic stimulation when the blood pressure was lowered by hemorrhage (Fig. 3B). It did not appear under this agent when the blood pressure was lowered by cardiac tamponade. The secondary discharge was easily elicited by sciatic stimulation under *light* pentobarbital anesthesia, *when the blood pressure was low*. When the blood pressure was normal it has been elicited only under deep pentobarbital anesthesia.

Bremer's view<sup>3</sup> that the difference between ether and the barbiturate depends on ether abolishing equally all elements of sensory response, while the barbiturate acts selectively on *after-discharge* (which he relates to intercalated neurones, located in the cortical network, connecting sensory and motor elements), explains some of these facts. It probably does not account for the striking effect of secondary discharge under deep barbiturate anesthe-

sia. This effect suggests that the barbiturate blocks ordinary streams of afferent impulses, perhaps simply raises thresholds in channels of approach to the cortex and thus "puts the cortex to sleep," as evidenced by smoothed base line; and that massive sensory stimuli (strong shock to sciatic), by virtue of number of simultaneous nerve impulses, break through the partial block and initiate the cortifugal discharge (or perhaps laterally spreading discharge) which constitutes the "spike." The fact that this is not evoked when the cortex is already active (in light barbiturate anesthesia) and its immediate subsidence on rapidly repeated volleys, indicates a "line busy" effect; i.e., when the mechanism is thrown into action it becomes refractory to further stimuli for nearly a second.

### SUMMARY

Concentric electrodes are described which are useful in studying the electrical changes in the brains of experimental animals. The grid lead is from a point within the cortex; the ground lead from the surface.

The typical cortical patterns found under ether and under pentobarbital anesthesia have been recorded at a constant level of anesthesia. The systemic arterial pressure has then been varied by means of cardiac tamponade and the cortical effects of this recorded.

At a constant level of anesthesia a fall in blood pressure is followed by cortical changes which are indistinguishable from those caused by an increase in the depth of anesthesia.

The similarity extends even to the appearance on sciatic stimulation of a secondary cortical discharge under pentobarbital anesthesia. Heretofore this secondary discharge had been evoked only under deep anesthesia. The phenomenon is briefly discussed.

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# INHIBITION AND IMPULSE SUMMATION AT THE MAMMALIAN NEUROMUSCULAR JUNCTION

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IN AN early stage of curarization, voluntary muscle still responds to an isolated volley of impulses sent over its motor nerve. A second volley 0.1 to 10 secs. later evokes a weaker twitch than did the first, and within limits the weakening is progressive if the series is continued (Rosenblueth and Morison, 1937). The first volley clearly leaves an inhibitory after-effect which is capable of being summated. It is not, however, simply a prolongation of the normal refractory period. If two volleys are timed only a few msecs. apart the response is greater than a single twitch (Bremer and Titeca, 1935); and when curarization is so far advanced that a single volley fails to excite, the muscle still responds if two are delivered in rapid succession. The inhibitory after-effect is therefore preceded in time by a briefer facilitation. The latter also is capable of summation to a limited degree; but on tetanic stimulation of the nerve there is only a transient initial contraction. This is followed by Wedensky inhibition, which can be maintained indefinitely.

During the junctional depression induced by magnesium salts there is likewise a stage at which motor volleys can excite the muscle by summation but not singly. In this condition, however, no inhibitory effect has apparently been described, nor has the facilitation left by the first volley been compared to that found under curare. In the recent work on chemical transmission, it has been inferred that curare blocks by rendering the receptive substance resistant to the exciting action of acetylcholine (Dale, Feldberg and Vogt, 1936; Rosenblueth and Morison, 1937). So far as we are aware, the Mg block has not been interpreted in terms of chemical transmission. It is reversible, in the mammal, by several agents antagonistic to curare, among them eserine, ACh, and potassium (Brosnan and Boyd, 1937).

This paper includes: (1) a comparison of the effects of Mg with those of curare, in respect to facilitation and inhibition at the neuromuscular junction; (2) a study of the effects of eserine, and of depressing doses of ACh, on the course of facilitation.

## PROCEDURE

Dogs under nembutal anesthesia (45 mg. per kilo) were used. The right sciatic nerve was sectioned, and one or two pairs of shielded electrodes were placed on either the peroneal or the tibial branch. The leg was immobilized by drills through the tibia. Contractions of the tibialis anticus or gastrocnemius muscle, pulling against a rubber band, were recorded, the lever excursion varying approximately in linear relation to the tension. The desired degree of depression was produced by slow intravenous administration either of  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$ , in 6.7 per cent solution, or of crude curare, 0.1 to 1.0 per cent, from a burette connected to the left femoral vein. Complete suppression of the response to single volleys usually required from 0.4 to 0.6 gm. per kilo of the Mg salt, or about 2 mg. per

kilo of the curare ordinarily used This curare was obtained from Peruvian Indians through the courtesy of a student, Mr E Salomone Another sample, from Burroughs, Wellcome and Co, showed no difference in action except in potency

For delivering paired stimuli separated by brief measurable intervals, we used the double condenser circuit described by Bernstein (1937) Stimuli of low frequency were supplied by a neon-tube circuit

### RESULTS

1. *The inhibitory after-effect.* Our observations on this phenomenon confirm, with respect to the curarized preparation, those of Rosenblueth and Morison (1937). If, after a period of rest, the nerve is stimulated at any frequency between 6 and 600 per min., the twitches become progressively weaker.



FIG 1 Responses of lightly curarized muscle (tibialis anticus), after one minute of rest, to stimulation of peroneal nerve at frequency of 10 per sec

The decline is more marked with increasing dosage of curare, or with an increase in frequency of stimulation within the range indicated. The authors cited suggest that successive quanta of acetylcholine (ACh), released at the same nerve ending, become progressively smaller. The later quanta of ACh in a series might then fall below threshold for an increasing number of muscle units. It may be pointed out, however, that the weakening of responses does not continue beyond the fifth or sixth twitch. After this, even at 10 per sec., a steady level is maintained or there is a slow rise (Fig. 1). There appears to be no direct evidence to indicate a corresponding variation in quanta of ACh. It is true that Dale, Feldberg and Vogt (1936) found a progressive diminution in the output of that substance from a perfused muscle during successive periods of stimulation of its nerve (frequency 5 to 15 per sec.). Each sample of perfusate assayed, however, contained the total amount of ACh liberated by several hundred volleys. Their data hardly justify an assumption that the second quantum falls sharply below the level of the first, particularly

under conditions of normal blood supply. The same authors found that curare does not alter the amount of ACh recovered after a given period of activity of the nerve. Any changes in quanta occurring under curare must therefore be presumed to be normal. But considering the resistance to fatigue, and the brief refractory period of the normal transmitting mechanism, it seems unlikely that a period of more than 10 secs. can normally be required, after a single impulse, for recovery to the resting state.

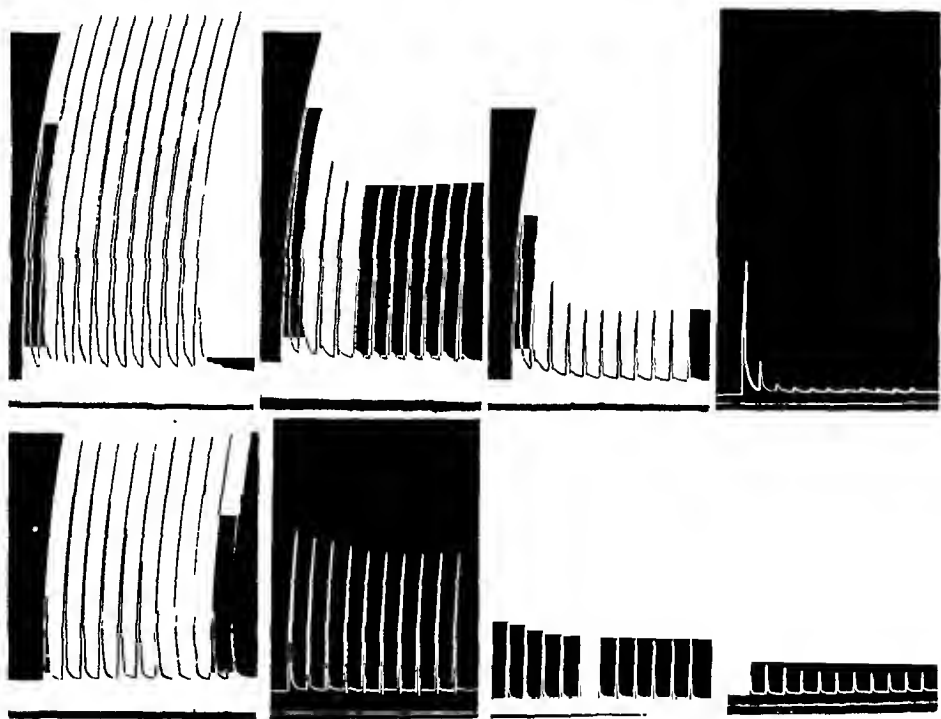


FIG. 2. Responses of *m. tibialis anticus* to stimulation of motor nerve, frequency 144 per min. Each series recorded after a rest of 20 secs. Showing behavior during progressive induction of junctional block by curare (above) and by  $MgSO_4$  (below).

In the corresponding stages of Mg depression there is no progressive weakening in a series of twitches unless the frequency is 30 per min. or higher. Even then the decline is much smaller and more gradual than that found under curare, the difference between the first and second twitches being just perceptible (Fig. 2). Lubinska (1935) found that after the single twitch response had been suppressed by Mg, a sustained tetanus could be built up by stimulating the nerve at a frequency of 27 per sec. We have confirmed this (Brosnan and Boyd, 1936), failing to find Wedensky inhibition with any frequency up to 120 per sec. Under Mg an abrupt decline in quanta either does not occur, or it does not influence appreciably the response of the muscle. If the inhibitory

after-effect is a normal process, its time course obviously is distorted either by curare or by Mg, possibly by both.

2. *Facilitation following a single volley.* By means either of curare or of Mg, the preparation was depressed until a single stimulus to the nerve evoked a barely visible twitch. A slow inflow into the vein was then so adjusted that this minimal response was constant. Pairs of stimuli timed at varying intervals were then applied, the first of each pair being supramaximal and the second considerably stronger. When curare was used, a rest of 15 secs. was allowed between pairs of stimuli, in order to avoid the inhibitory effect. With Mg the usual interval was 10 secs. A complete time curve of facilita-

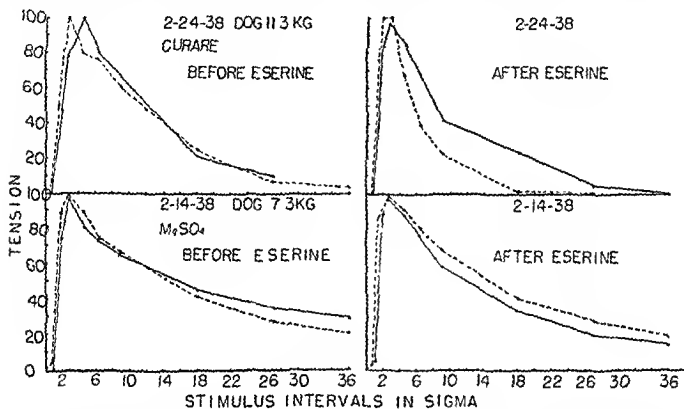


FIG. 3. Tension of summated muscle response plotted against intervals between paired stimuli, before and after eserine. Above, under curare; below, under Mg. Further explanation in text.

tion (tension plotted against time interval between first and second stimuli) was determined repeatedly on each animal, curare being used with 4 dogs and Mg with 6.

In about half the experiments, a summated response was obtained with stimuli timed only 0.9 msecs. apart. The maximum usually fell between 2 and 3 msecs. Small variations were found even when successive measurements were made on the same animal. These were probably due mainly to variations in the threshold of the nerve during the relative refractory period, and to the difficulty of maintaining a perfectly uniform state of curarization. The form of the curve is similar to that described by Bremer and Homès (1932) for the curarized frog, though the mammalian curve is briefer. Its course is approximately the same whether curare or Mg is used (Fig. 3). The rectal temperature did not vary more than 1°C. in any experiment.

3. *Absence of facilitation during Wedensky inhibition.* The lightly curarized preparation was maintained in partial or complete Wedensky inhibition by stimulating the nerve at a low frequency, 60 to 150 per min. During this time, paired stimuli 2.5 to 5.0 msecs. apart were applied through a second pair of electrodes on the nerve. The resulting response was summated either poorly or not at all, according to the degree of Wedensky inhibition existing at the time (Fig. 5A and B).

When the single twitch responses are reduced to a correspondingly low level by Mg, however, stimulation of the nerve through one pair of electrodes

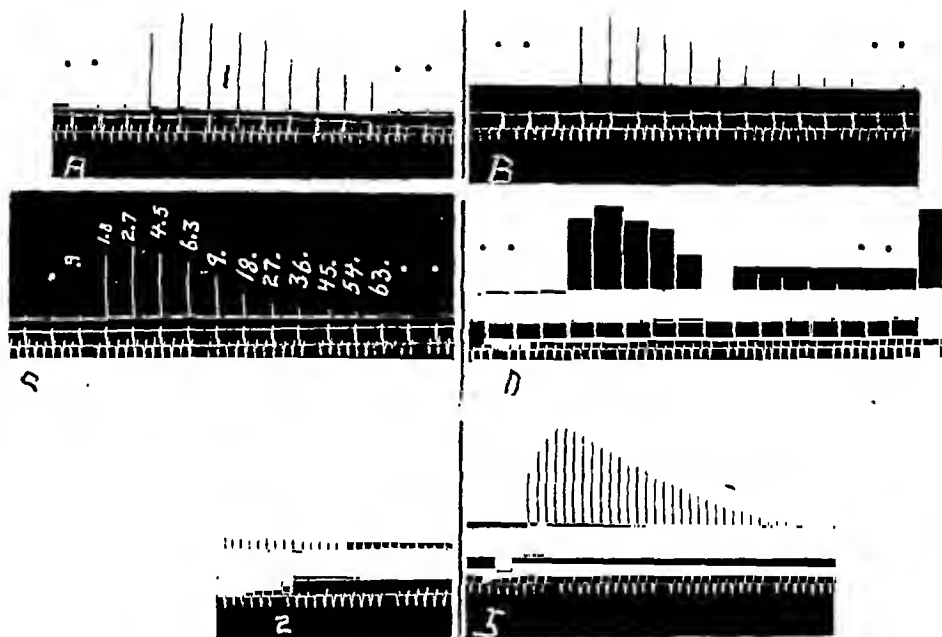


FIG. 4. Dog, 7.3 kg., nembutal, Mg. Gastrocnemius-soleus excited through tibial nerve. A and B, before eserine; C, 11 minutes after 5 mg. each of physostigmine salicylate and atrophine sulphate; D, 5 minutes after a second equal dose. Dots indicate responses to single stimuli (1 and 2) all others double. Stimulus intervals, in each series, are 0.9, 1.8, 2.7, 4.5, 6.3, 9.0, 18.0, 27.0, 36.0, and 45.0 milliseconds, in the order given. In D, the final twitch is a response to 2 stimuli 2.7 ms. apart, and duplicates the maximum of the series.

Below, same animal, single stimuli throughout at 5-second intervals. Signal 2, injection of 2 mg. of ACh, before eserine; 5, same after completion of series D above.

at the rate of 150 per min. does not prevent a summated response to two closely timed stimuli applied through a second pair of electrodes (Fig. 5C). This indicates again that the inhibitory process dominates junctional behavior under curare, but is absent or minimal under Mg.

4. *The effect upon facilitation of depressing doses of acetylcholine.* Rosenblueth, Lindsley and Morison (1936) found that acetylcholine in large doses, particularly after eserine, weakens or suppresses completely the response of muscle to indirect stimulation. If facilitation is a summation of quanta of

ACh, as suggested by Rosenblueth and Morison (1937), paired stimuli, applied to the nerve during this depression, should be no more effective in exciting the muscle than single shocks; for any ACh released by the first volley of impulses would add to the depressing concentration already existing.

We first administered eserine (0.5 to 1.0 mg. per kilo). This caused the usual potentiation of twitch responses to single volleys at 8 to 10 sec. intervals. At such a slow frequency of stimulation we were unable to suppress the twitch responses completely by any dosage of ACh up to 1 mg. per kilo (intravenous). On increasing the frequency of test stimuli to 2 per sec., the

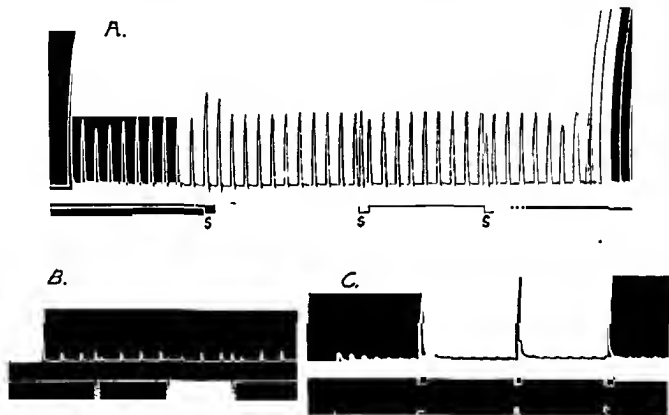


FIG. 5. Paired stimuli 2.7 milliseconds apart applied to peroneal nerve at down stroke of each signal, while low-frequency stimulation was being maintained through a second pair of electrodes. A, in early curarization; B, same animal, deeper curarization; C, another animal, after twitch responses had been nearly suppressed by  $MgSO_4$ . Twitch frequencies, in A, 3 per sec., in B, 1, and in C, 2.5 per sec. Summation well marked in C, feeble in A, absent in B.

twitches were nearly or completely suppressed; and during the depression two closely timed stimuli applied through a second pair of electrodes failed to evoke a summated response (Fig. 6). This is perhaps negative evidence in favor of the theory that facilitation is a summation of quanta of ACh; but as shown above, the curarized preparation behaves in the same way under similar conditions of stimulation. In both conditions, the absence of facilitation is associated with a low-frequency Wedensky inhibition.

5. *The effect of eserine on the time course of facilitation.* After carrying out the procedure described in section 2 above, we administered to the same animals 0.5 mg. per kilo of physostigmine salicylate, with an equal dose of atropine sulphate. This decurarized, but the original state of block was re-

stored by administering additional Mg or curare. The time curve of facilitation was then again determined. Typical curves are shown in Fig. 3, and graphic records in Fig. 4. In a few instances the period of effective summation was found shorter after eserine than before; usually the two curves nearly coincided. Once the maximum fell later (at 4.5 ms.) after eserine than before (3.0 ms.) but the descending portion of the curve was never prolonged. We found, though not constantly, the shortening of the minimum summation interval noted by Bremer and Kleyntjens (1937).

The last-named authors report that eserine does not prolong the period of impulse summation in the curarized frog. Eccles (1935) had previously reported a failure of eserine to prolong facilitation in the superior cervical ganglion of the cat, and concluded that summation of quanta of ACh could not be the mechanism of facilitation in the ganglionic synapses. Cannon and Rosen-

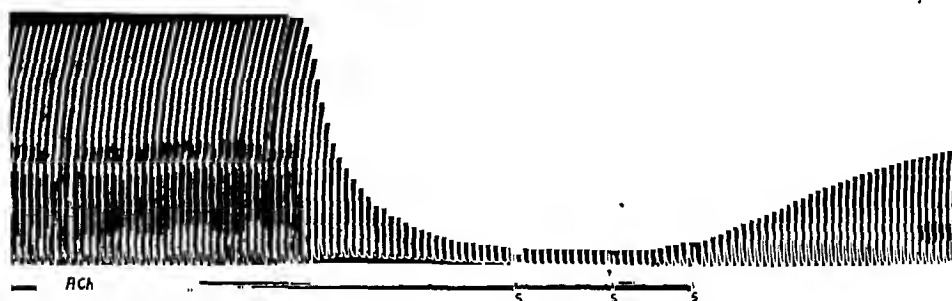


FIG. 6. Dog, 14.5 kg., nembutal. Eserine and atropine (7 mg. of each) 7 minutes before beginning of record. Twitches of *m. tibialis anticus*, in response to stimulation of peroneal nerve at frequency of 2 per second. ACh, intravenous injection of acetylcholine, 4 mg. At each signal S, paired stimuli 4.5 milliseconds apart were applied through a second pair of electrodes.

blueth (1937) object to this conclusion, on the ground that Eccles' records may have been made after an interval long enough for the anticholinesterase activity of the eserine to have disappeared. In the experiments of Bremer and Kleyntjens, a single dose of curare was administered to each frog. When the desired stage of curarization had been reached, the time curve of facilitation was determined. Eserine was then administered, with a temporary decurarizing effect; but the preparation soon lapsed into the original state of curarization and the records were repeated. The authors assume that the return of junctional block after eserine was not due to disappearance of the effect of that agent, but to a continued progressive action of the curare. While this assumption may have been correct, it would seem desirable to supply more direct evidence about the duration of the effect of eserine.

In our experiments, a period of 10 to 25 mins. elapsed, after eserine, before the animal was recurarized to the desired constant state. A second equal dose of eserine could then be given, however, with little or no decurarizing action.

As a routine, we made one series of records of facilitation after the first dose of eserine, and repeated the procedure within 10 minutes after the second dose. Both sets of records thus obtained were quite similar to those made before eserine (Figs. 3 and 4). Finally, we regularly administered two equal doses of ACh, 0.2 to 0.4 mg. per kilo, one before eserine and the other after completing the final series of facilitation records. The decurarizing action of the second dose was always greater and more prolonged than that of the first (Fig. 4).

### DISCUSSION

It seems to us that latent addition at the neuromuscular junction cannot be attributed to summation of quanta of ACh. The question is discussed at length by Bremer and Kleyntjens (1937) who suggest that the first blocked impulse sets up a subliminal excitatory state in the muscle; that this excitatory state dies away gradually, and while it persists may be raised to threshold value if a second similar process is superimposed. The authors cited consider that this view is compatible with the theory that acetylcholine is the essential transmitter, since the cellular excitatory process might be set up by a quantum of ACh. But eserine restores the response of the curarized preparation to a single volley. If this effect is due to its anticholinesterase activity, it follows that the excitatory state assumed by Bremer and Kleyntjens varies in intensity according to the amount of ACh acting; and it is still difficult to see why eserine should not prolong the period of facilitation, unless the destruction of each quantum of ACh is so rapid that summation, even after eserine, is impossible.

It may be objected that in our experiments (also in those of Bremer and Kleyntjens) recurarization after eserine raised the threshold of the muscle for ACh; and that although the period for summation of two quanta may actually have been prolonged, this effect was nullified because summation had to reach a higher level than before in order to excite the muscle. Such an objection, however, can hardly be maintained. If the threshold was raised by the additional curare or Mg, eserine had also raised the level reached by a single quantum, so that the relation between the first quantum and the threshold was the same as before. The increment added by the second quantum must have been correspondingly increased after eserine, so that it should have reached threshold value so long as any considerable residue was left from the first. This presumes that the first and second quanta are equal, or nearly so. If the second is much smaller than the first, as Rosenblueth and Morison suggest, comparison of the facilitation curves before and after eserine becomes more complicated; but as was pointed out in section 1 above, there is no convincing evidence that such a disparity exists.

We have used the terms "impulse summation" and "facilitation" interchangeably. Bremer and Kleyntjens (1934) use the latter term to designate an enduring after-effect of manifest activity in synapses; the former they apply to a subthreshold junctional effect left by one or more impulses which fail to be transmitted. Impulse summation or latent addition they consider to



be a relatively brief process. But such a distinction is difficult to apply to the neuromuscular junction. Tetanic stimulation of a motor nerve in the curarized mammal may fail to excite the muscle, and yet leave a facilitation lasting for several minutes (Boyd, 1932).

### SUMMARY

1. When the nerve of a lightly curarized mammalian preparation is stimulated at any frequency from 6 to 600 per min., the second muscle twitch is weaker than the first and a sustained Wedensky inhibition of some degree follows (confirming Rosenblueth and Morison).

2. During corresponding stages of neuromuscular depression produced by magnesium salts, the inhibitory effect of repeated stimulation is much less in degree, and of shorter duration, than under curare.

3. When the response to a single volley of impulses has been completely suppressed by Mg, the muscle can still be excited if two stimuli are applied to the nerve in rapid succession. The junctional summation of the two volleys follows a time course closely resembling that found under curare.

4. The depression of neuromuscular transmission produced by excessive concentrations of acetylcholine is a low-frequency Wedensky inhibition, resembling in its time relations that of the lightly curarized preparation. In both of these conditions junctional summation of two closely timed volleys is ineffective. During Mg depression, however, low-frequency stimulation of the nerve at one point does not prevent a summated response to two volleys set up elsewhere on the nerve.

5. Under curare, the period for effective junctional summation of two volleys is not prolonged following administration of eserine, with recurarization to the original state of block (confirming Bremer and Kleynjens). The result is also negative if Mg is substituted for curare. The failure of eserine to prolong the summation period is not due to rapid disappearance of its anticholinesterase activity.

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# AUTONOMIC ACTIVITY AND BRAIN POTENTIALS ASSOCIATED WITH "VOLUNTARY" CONTROL OF THE PILOMOTORS (*MM. ARRECTORES PILORUM*)

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THE CONTROL of most of the functions of the autonomic nervous system is generally considered to be "involuntary" in character. A few cases have been described, however, in which one or another of the autonomic activities is under "voluntary" control. Most of these deal with some aspect of the visual mechanism, such as, "voluntary" control of accommodation,<sup>2,3,16,17</sup> pupillary dilatation<sup>14</sup> and constriction.<sup>11</sup> The case to be described here is of particular interest since it involves "voluntary" control of the *arrectores pilorum* muscles which are innervated only by the sympathetic division of the autonomic nervous system.

The subject is a middle-aged male, who since the age of 10 years has been aware of the ability to control the erection of hairs over the entire surface of his body. Experimental study of the subject has revealed that the erection of hairs is accompanied by a number of other autonomic phenomena of which he was not aware. These consist of an increase in heart rate, an increase in the rate and depth of respiration, dilatation of the pupils, an increase in the electrical potentials of the skin over regions rich in sweat glands and characteristic changes in the electrical potentials over the premotor area of the brain.

## METHODS

Sixteen millimeter motion picture records, at a measured speed of 18 frames per second, were made of the erection of the hair on the dorsal surface of the forearm, the lateral surface of the thigh, and the anterior surface of the leg just below the knee. Similar records of the dilatation of the pupil, which occurs during "voluntary" erection of the hair, were made while the eye was illuminated by a 500 watt flood lamp at an angle of approximately 45° to the anterior surface of the cornea. Fixation of the eyes was always maintained on a point 15 feet away. A quick movement of the experimenter's hand before the lens of the camera marked the film and served as a signal for the subject to begin the erection of the hair; the same movement repeated meant to lower the hair. The movement fell on the periphery of the visual field and did not intercept the line of regard. The signals used in other aspects of the study consisted of a barely audible "click" in a headphone and the "flash" of a dim light. Control experiments in every case indicated that none of the effects observed was due to the stimulus value of the signals themselves.

Simultaneous recording of electrical phenomena, such as the electrocardiogram and skin potentials, or brain potentials from two regions on the surface of the head, was accomplished by means of two independent amplifying and recording systems. The amplifiers are of the resistance-capacity coupled type, with pre-amplifiers employing balanced input circuits. The time-constant of the amplifiers may be made appropriate to the particular type of phenomena to be recorded by changing the inter-stage coupling capacity (0.1, 0.5, or 2.0 mfd.). A type-PA Westinghouse oscillograph with matched elements served as the recording unit. The mechanical devices for recording respiration and changes in blood pressure are incorporated in the oscillograph case so that all phenomena may be recorded simultaneously on the same record if desired. Continuous changes in blood pres-

sure were recorded with the pressure in the cuff on the arm maintained at 70 to 80 mm. of Hg for short periods of time. Systolic and diastolic readings by the auscultatory method were also made before and during the erection of the hair.

Electrodes for recording brain and skin potentials consisted of small gold discs, 8 mm. in diameter, each sunk in a small bakelite block. The cup of the block was filled with an electrode jelly which served as the conducting medium. When brain potentials were recorded the electrodes were attached to the surface of the scalp, one to two inches apart, and held in place by bandages. For the recording of skin potentials the electrodes were attached to the palmar surface of the hand. Small silver plates and electrode jelly applied to the left wrist and ankle furnished leads for the electrocardiogram. Electrograms from individual arrectores pilorum muscles were obtained by means of needle electrodes inserted through the skin at the base of a hair on the side toward which it leaned. The needle electrodes consisted of a fine gauge hypodermic needle with either one or two fine insulated wires cemented in its lumen. When the first type was used the exposed tip of the single inner wire led to grid and the sheath of the needle to ground; in the latter case the exposed tips of the two wires led to the balanced input of a pre-amplifier and the sheath of the needle was grounded.

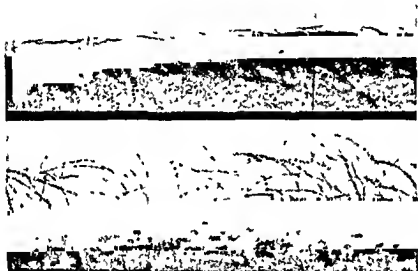


FIG. 1. "Voluntary" erection of the body hairs. Sections from a motion picture record of the hair on the lateral surface of the thigh, before the signal to erect the hairs and about 10 seconds after the signal showing the hairs erect and the "gooseflesh" appearance of the skin.

## RESULTS

Several series of experiments have been made in which the erection of the hair on the arms and legs was photographed. Fig. 1 shows two frames from a motion picture record of the erection of the hair on the thigh. The first shows the hair in its normal position close to the surface of the skin before the signal to erect the hairs. The second, taken approximately 10 secs. after the signal, shows the hairs almost fully erected and the "gooseflesh" appearance of the surface of the skin.

Fig. 2 shows three frames from a motion picture record of the dilatation of the pupil which accompanies the "voluntary" erection of the hairs. The first is from a section of the record before the signal to erect the hairs and shows the pupil well constricted. The second shows the increased diameter of the pupil while the hairs are erect; the third shows the decreased diameter



FIG. 2. Dilatation of the pupil during "voluntary" erection of the body hairs. Sections from a motion picture record before, during and after the erection of the hairs.

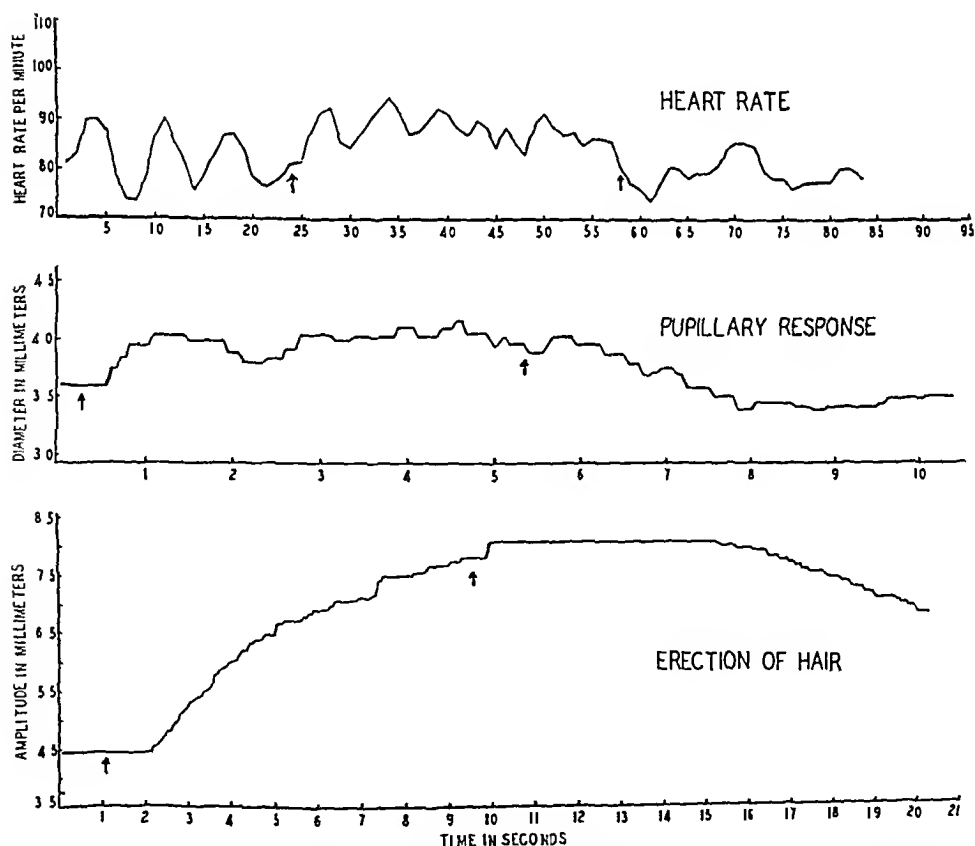


FIG. 3. Graphs showing changes in the heart rate, diameter of the pupil and the distance of a hair from the surface of the skin following a signal (first arrow) to erect the hairs and a signal (second arrow) to lower them.

a few seconds after the signal to lower the hairs. Frame by frame analysis of the motion picture records under magnification in an Edinger projector revealed that the hairs began to rise approximately 1 sec. after the signal was given. By plotting the distance of the tip of any hair from the surface of the skin in successive frames (see Fig. 3) it was found that the erection of a hair proceeds in a step-wise fashion. Maximum elevation of a number of hairs studied was attained in about 7 secs. After a signal to lower the hairs was given 5 to 6 secs. elapsed before actual lowering occurred. The lowering of the hairs also proceeded by steps and was completely accomplished between 15 to 20 secs. after the signal to lower them.

The degree of illumination necessary for photographing the pupils caused considerable constriction which competed with the dilatation accompanying

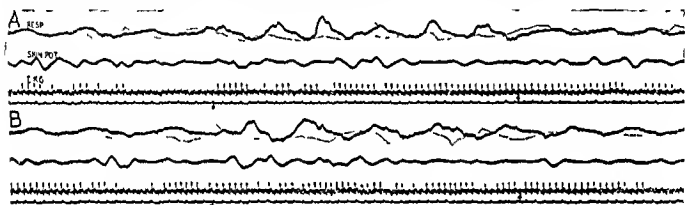


FIG 4 Simultaneous records of heart rate (E.K.G.), respiration and skin potentials from the palm of the hand showing distinct changes during the "voluntary" erection of the body hairs. The dotted line is a continuous record of changes in heart rate, an increasing rate is shown by a descent of the line. The first arrow represents the signal to erect the hairs, the second to lower them. Time is shown in seconds at the bottom of each record.

the "voluntary" erection of the hairs. The pupils at the start of an experiment usually ranged from 3 to 3.5 mm. in diameter. Dilatation of the pupils (see Fig. 3) began 0.3 to 0.5 of a sec. after the signal to raise the hairs. Maximum enlargement of the diameter under these conditions of high illumination ranged from 0.5 to 1.5 mm. and was usually attained in 0.5 of a sec. Enlargement of the pupils was maintained throughout the duration of the erection of the hairs at a level well above the starting diameter, although there were frequent fluctuations due to the competing tendencies for dilatation and constriction. Five-tenths of a sec. after the signal to lower the hairs the pupils began to constrict in a step-wise manner. Constriction always proceeded to a level below that of the original diameter of the pupils but slowly returned to it.

Simultaneous records of heart rate (electrocardiogram), respiration and skin potentials from the palm of the hand (see Fig. 4) show that changes in these phenomena occurred approximately 1 sec. after the signal to erect the hairs. The dotted line in these records gives moment to moment heart rate values which were obtained by measuring the interval between successive R-waves of the electrocardiogram with proportional dividers adjusted to mul-

tively by 10 and erecting an ordinate over the midpoint of each interval. A typical curve of heart rate changes during the erection of the hairs is shown in Fig. 3. Heart rate, which oscillates widely during the two phases of respiration, was maintained at a definitely higher level while the hairs were erect than before they were raised or after they were lowered. During the "voluntary" erection of the hairs the heart rate was increased by 6 to 8 per cent; respiration was increased by 9 to 25 per cent in rate and by approximately 100 per cent in depth. Anticipation of the signal frequently increased the skin potentials in the palm of the hand but the degree of activity was usually distinctly increased about 1 sec. after the signal to raise the hairs.

Fig. 5 shows electrograms obtained from individual arrectores pilorum muscles by means of needle electrodes during the "voluntary" erection of

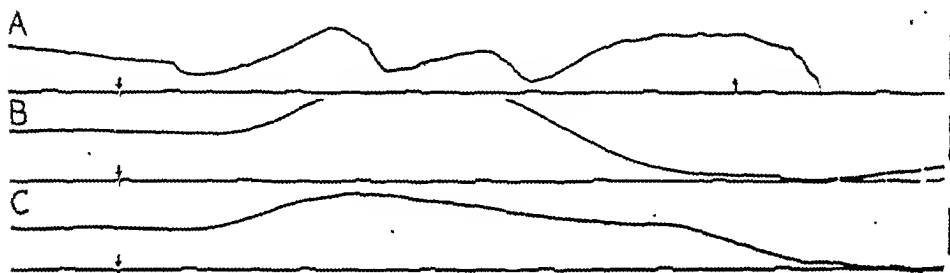


FIG. 5. Electrograms from individual arrectores pilorum muscles during "voluntary" elevation of the body hairs. The first arrow indicates the signal to erect the hairs, the second to lower them. Time is shown in seconds at the bottom of each record. Calibrations at right of each record equal 150 microvolts.

the hairs. The electric response occurs from 0.5 to 0.7 of a sec. after the signal to raise the hairs and thus precedes the mechanical movement of the hairs which has a latency of about 1 sec. As shown in Fig. 5, the electric response may consist of rhythmic oscillations (A), or long, slow undulations (B and C). Occasionally small, quick, spike-like components are superimposed. Both the rhythmic and the more prolonged electric responses have been described in smooth muscle by Lambert and Rosenblueth,<sup>13</sup> Rosenblueth, Davis and Rempel,<sup>15</sup> and by Eccles and Magladery.<sup>6,7</sup> The electric responses shown here seem to correspond in time relations to the slow component III described by Lambert and Rosenblueth,<sup>13</sup> but there is no "initial complex" corresponding to their components I and II. Since, for the purposes of this study, latency is the main concern, further analysis of the response will not be attempted here.

Continuous records of the relative changes in blood pressure have shown that there is a very slight increase during the "voluntary" erection of the hairs. Repeated readings by the auscultatory method have shown that there are also very slight elevations of the diastolic and systolic pressures. Although the changes were always in the direction of an increase they have for the most part been too small to be considered significant.

Electrical potentials of the brain were recorded simultaneously from over two regions of the same hemisphere during "voluntary" erection of the hairs, usually from the premotor and occipital, premotor and temporal, premotor and parietal, or the premotor and the anterior part of the frontal region. Characteristic responses consisting of large, slow waves were found only over the premotor region (see Fig. 6). The latency of the electric response of the premotor region ranges from 0.23 to 0.35 of a sec. There is sometimes an "off response" 0.2 to 0.3 of a sec. after the signal to lower the hairs. The general pattern of the premotor response is essentially the same on repetition of the experiment. The largest response is obtained when the electrodes are over a region just anterior to the central sulcus, in a line parallel with, but about 1 inch off the mid-line. According to careful estimate by Chiene's

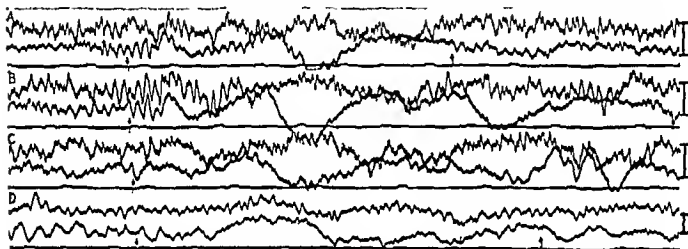


FIG 6 Electrical potentials of the brain simultaneously recorded from over the premotor (middle line of each record) and occipital (upper line) areas during "voluntary" erection of the hairs. In A, B, and C the premotor electrodes were over the upper part of  $6a\alpha$ , in D they were over the upper part of  $6a\beta$ . The first arrow indicates the signal to erect the hairs, the second to lower them. Time is given in seconds at the bottom of each record. Calibrations at the right of each record equal 20 microvolts.

method<sup>5</sup> for determining the relationship between cranio-cerebral topography, the area between the electrodes probably included, mainly, the upper part of area  $6a\alpha$  and parts of areas 4 and  $6a\beta$ . Responses were obtained from over the outlying regions of  $6a\alpha$  and  $6a\beta$  but they were never as prominent as those from the upper part of  $6a\alpha$ .

The nature and direction of the various changes in autonomic activity associated with the "voluntary" erection of the hairs, together with the general concurrence of these changes suggest that there is a generalized sympathetic discharge. The fact that marked changes in the brain potentials occur only over the premotor area and precede the peripheral autonomic phenomena further suggests that the premotor cortex plays a part in the generalized sympathetic discharge associated with the "voluntary" erection of the body hairs.

#### DISCUSSION

The question arises as to how the subject is able to control the erection of the body hairs. So far as he is aware the process is essentially similar to



that of initiating contraction in one of his skeletal muscles. He does not call up an image of a painful or fearful experience as has been reported in connection with one case of so-called "voluntary" control of pupillary dilatation.<sup>14</sup> There is no straining or tensing of skeletal muscles and there are no observable movements of any sort. The subject is able to erect the hairs when in any position and while carrying on other activities. Of special importance is the fact that he is able to inhibit the reflex erection of the hairs and the appearance of "gooseflesh" normally induced by stepping out of a hot shower into a cold draft.

In this case, as in some of the others which have been described, "voluntary" control of an autonomic function was first discovered during childhood; either during severe fatigue, a critical illness or some other unusual condition. It may be that, unknown to these subjects, some form of conditioning took place when, under unusual circumstances, their attention was first called to the reflex manifestation of an autonomic function. Cason<sup>4</sup> and Hudgins<sup>11</sup> have shown that pupillary constriction may be conditioned to an auditory stimulus. Hudgins has even demonstrated that pupillary constriction originally induced by a light stimulus may be conditioned to the command "constrict" or even to the subvocal production of verbal stimuli by the subject himself. This has led Hunter and Hudgins<sup>12</sup> to offer the hypothesis that all so-called voluntary behavior is a form of conditioned response.

With respect to the subject described here there is no satisfactory evidence that he did not always have the ability to erect the hairs nor is there evidence that some form of conditioning took place when he first noticed the ability.

No matter how the "voluntary" control of the pilomoters is brought about in this case the familiar tendency of the sympathetic system to respond as a whole is apparent in the accompanying phenomena. The latencies of these various responses are of such an order as to indicate that they are a part of a generalized discharge of the sympathetic system. The finding of characteristic brain potential changes over the premotor area suggests that they are precursors of the peripheral autonomic changes. This corresponds with the results from experiments on animals<sup>8,9,10,18</sup> and human subjects<sup>1</sup> which have indicated that there is an autonomic representation in the cortex, particularly in the premotor area.

#### SUMMARY

A subject has been described who has "voluntary" control of the pilomoters (*arrectores pilorum* muscles). Experimental study of the subject has revealed that the "voluntary" erection of the body hairs is accompanied by an increase in heart rate, an increase in the rate and depth of respiration, dilatation of the pupils, an increase in the electrical potentials of the skin over regions rich in sweat glands, and a very slight increase in blood pressure. The nature and direction of these changes together with their latencies indicate a tendency for a generalized sympathetic discharge.

Simultaneous records of electrical potentials from two regions of the brain,

the premotor and one of the other regions, during the "voluntary" erection of the body hairs have shown characteristic changes only over the premotor area. These premotor responses precede and appear to be associated with the peripheral autonomic changes. This has been interpreted as further evidence of the representation of the autonomic nervous system in the premotor area of the cortex.

The possibility that the subject's ability to control the erection of the hairs is the result of a conditioning process has been discussed, but no satisfactory evidence for or against this hypothesis is at hand.

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# THE INFLUENCE OF HYPOTHALAMIC STIMULATION ON INTESTINAL ACTIVITY

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It is the purpose of this study to investigate the functions of the hypothalamus in regulating the motility and blood supply of the small intestine in relation to the other vegetative, emotional and mimetic reactions produced by the electrical stimulation of the diencephalon, or by the injection of strychnine sulphate into its nuclei.

## METHODS\*

Fourteen cats were prepared in two series of experiments as follows:

*Acute experiments (8 animals).* The experiment was usually performed approximately 6 hours after the animal had been fed. Ether anesthesia through an intratracheal cannula was maintained at a level just deep enough to abolish spontaneous movements. With the Horsley-Clarke stereotaxic instrument† in place and an electrode inserted into the hypothalamus, the animal was mounted in an upright position in a hammock provided with holes for the legs and the exposed gut. The blood pressure in the right common carotid artery and the respirations were recorded on a kymograph in the usual manner above the tracings of a signal magnet and a one-second timer. A wide, shallow beaker containing Ringer's solution kept at a temperature of about 39°C. was then arranged so that the dependent portions of the jejunum and ileum were supported just outside the incised and dorsally displaced abdominal wall, thus preventing traction on the mesentery and interference with the blood supply of the intestines. Under these conditions, peristalsis, rhythmic segmentation and pendular movements of the gut were easily observed, although in some animals the small intestine seemed entirely motionless for varying periods. The animal's temperature was maintained at a normal level by warming the Ringer's solution continuously and by the use of an electric heating pad applied to the animal's back when necessary. Cats prepared in this manner remained in good condition for as long as 5 hours with little change in reactivity to repeated electrical stimulation of the hypothalamus except as induced by the administration of strychnine.

*Recovery experiments (6 animals—23 experiments).* In a cat anesthetized with pentobarbital sodium, a bipolar needle electrode was inserted by means of the Horsley-Clarke stereotaxic instrument into the hypothalamus and then firmly cemented in position to the skull. In 8 to 24 hours the animal usually recovered completely from the operation and could then be observed in an unanesthetized, untrammelled state for the effects of electrical stimulation of the hypothalamus before or after the injection of this structure with solutions of strychnine sulphate or other substances. In preparation for fluoroscopy, the animal was given 100 cc. of an opaque mixture (barium sulphate suspended by mucilage

\* The various techniques employed in preparing animals for the stimulation or injection of the diencephalon have been described in detail in earlier communications from this laboratory. See MASSERMAN, J. H.: Effects of sodium amylal and other drugs on the reactivity of the hypothalamus of the cat. *Arch. Neurol. Psychiat.*, Chicago, 1937, 37: 617-628. MASSERMAN, J. H.: The effects of the destruction of the hypothalamus of the cat on its activity and on the pharmacologic action of sodium amylal. *Arch. Neurol. Psychiat.*, Chicago. In press.

† HORSLEY, V., and CLARKE, R. H.: The structure and functions of the cerebellum examined by a new method, *Brain*, 1908, 31: 45-124. CLARKE, R. H., and HENDERSON, E. E.: *Investigations of the central nervous system: methods and instruments*. Baltimore, Johns Hopkins Press, 1920. RANSON, S. W.: On the use of the Horsley-Clarke stereotaxic instrument, *Psychiat. en neurol. bl.* (Feestb. C. H. Ariëns Kappers), 1934, 38: 534-547 (May-Aug.).

of acacia in water) from 30 to 60 minutes before experimental observations were made. Fluoroscopy was done approximately 24 hours after operation and again after 48 hours if the animal's rectal temperature had not reached 105°F. At the time of the first examination the pyloric antrum and the entire small intestine were usually well visualized and showed active rhythmic segmentation and peristalsis.

**Stimulation** For electrical stimulation of the hypothalamus, a Harvard inductorium carrying three volts across the terminals of the primary coil or a 60 cycle alternating current reduced by a series of variable resistances to from 0.5 to 9.0 volts was employed. The effects of bipolar (highly localized) and unipolar (diffusing) stimuli were observed before and after the injection of strychnine sulphate into the hypothalamus in both acute and recovery preparations.

**Injections** Selected amounts of strychnine sulphate were dissolved in 0.05 to 0.1 cc. of water and injected into the hypothalamus at the rate of 0.1 cc. per min. Dosages of from 0.07 to 0.20 mg. per kilogram were given, the smaller dosages usually being repeated in from 30 to 60 minutes.

**Anatomic studies** After the terminal experiment the brain was fixed in a 10 per cent solution of formaldehyde and the region of the hypothalamus sectioned serially and stained in alternate sections for nerve fibers by a modified Weil technique and for nerve cells by the Nissl method. The sections were then examined to determine accurately the nerve structures that had been stimulated and injected.

**Sites of stimulation and injection** Most of the observations (7 animals in the acute series, and all 6 of the recovery preparations) were made with the electrode at coordinate settings of from 2.0 to 2.5 mm. to the right of the midline, from 10.0 to 12.5 mm. anterior to the interaural frontal plane and from 4.0 to 6.0 mm. below the zero horizontal plane of the stereotaxic apparatus. The structures directly affected by stimulation and injection were the rostral tip of the H<sub>1</sub> field of Forel, a portion of the substantia nigra, the lateral margin of the nucleus filiformis principalis, the nucleus perifornicalis, the nucleus hypothalamicus anterior, the upper and lateral edge of the nucleus supra opticus diffusus, the dorsal hypothalamic area and the rostral one-third of the nucleus hypothalamicus lateralis\*. In 5 animals, the same region in the left hypothalamus was also studied and in a number of others more extensive explorations were made in structures that will be specified when the results of stimulation and injection are described.

## RESULTS

### *Acute experiments*

In animals anesthetized with ether the average strengths of current necessary to produce responses to stimulation of the hypothalamus were obtained at the secondary coil setting of 10 cm. on the Harvard inductorium or at AC voltages of 3.0 V. for bipolar and 2.0 V. for unipolar stimulation. When these stimuli were employed in animals in which the exposed gut had been quiescent, rhythmic segmentation and peristalsis appeared in about 5 secs. and persisted for about 10 secs. after the period of stimulation (usually 15 secs.) was terminated; this series of responses could be elicited repeatedly. In addition, pendular, swaying and coiling movements of the gut with almost identical periods of latency and persistence were initiated by hypothalamic stimulation in seven animals and augmented when spontaneously present in one. Segmentation and peristalsis usually appeared and disappeared together, but the pendular movements could be elicited independently. However, in

\* The anatomic terminology used throughout this paper is adopted from INGRAM, W. R., HANNETT, F. I., and RANSON, S. W.: The topography of the nuclei of the diencephalon of the cat, *J. comp. Neurol.*, 1932, 55: 333-394. More extensive charts of the Horsley-Clarke coordinates of anatomic structures may be found in CLARKE, R. H., and HENDERSON, E. E.: Atlas of photographs of sections of frozen cranium and brain of the cat, *J. Psychiat. Neurol.*, 1911-12, 8: 119-156.

no instance were rhythmic segmentation, peristalsis, or pendular movements diminished by stimulation in this region of the hypothalamus with the strengths of current specified nor did the general tonicity of the small intestine seem to be affected. Both dilatation and constriction of the blood vessels in the intestine were observed to follow stimulation of the hypothalamus in various experiments, but more frequently there were no visible changes and cyanosis was never produced.

*General effects.* Accompanying these enteric reactions were other evidences of mild autonomic stimulation: partial dilatation of the pupils, contraction of the nictitating membranes, widening of the palpebral fissures, an elevation in blood pressure of from 5 to 30 mm. of mercury and an increase in the rate and depth of the respiration. Responses of the skeletal musculature consisted in slight movements of one or more of the extremities, twitching of the ears, closure of the jaws and occasionally, torsion of the head and neck. These bodily movements sometimes slightly displaced the intestines, but segmentation, peristalsis, and pendular movements in the absence of hypothalamic stimulation were not induced by respiratory excursions nor by moving the gut loops about in the beaker.

*Stimulation of other regions of the diencephalon and mesencephalon.* Segmentation and peristalsis of the intestine could be elicited by stimulating either side of the tuber cinereum or the dorsal portion of the supramammillary decussation. Similarly, pendular movements were induced or enhanced by stimulation in and above the middle portions of the mammillary bodies and in the supramammillary decussation and its nucleus. In contrast, diminution or abolition of intestinal movements followed stimulation with relatively weak currents in the suprachiasmatic region and in the supramammillary decussation 2 mm. below the point at which pendular movements had been obtained. Stimulation in the suprachiasmatic region also led to generalized spasticity and blanching of all of the visible intestinal loops—an effect which, in some animals, persisted until stimulation in the tuber cinereum brought a return of activity. Dilatation of the intestine was not observed in any of the experiments.

*Effects of stronger stimuli.* When the hypothalamus was stimulated with currents intense enough to elicit marked emotional mimetic responses (secondary coil settings of 8 to 7 cm. or 6 to 7 volts AC for bipolar and 3 to 4 volts for unipolar stimulation) intestinal motility, when spontaneously present, was either definitely reduced or stopped during the period of stimulation and for several minutes thereafter. In animals in which the gut had been motionless before stimulation of the hypothalamus with these strengths of current, no activity appeared during or following the stimulus, even though weaker currents applied to the same point in the hypothalamus had previously been effective in eliciting vigorous intestinal movements. In general, the tonus of the muscle wall of the intestine appeared to remain unchanged even with strong stimuli, although in one instance spasticity was observed. Similarly, the tonicity of the blood vessels in the gut wall usually seemed un-

affected except when spasticity of the intestinal musculature itself induced blanching. However, in those animals in which transitory engorgement or constriction of the vessels had been elicited by weak stimuli, the use of stronger currents led to a corresponding increase in the vasomotor responses.

*Effects of the injection of strychnine into the diencephalon.\** When 0.05 cc. of a solution containing 0.07 to 0.08 mg. per kilogram of strychnine sulphate was injected into either side of the tuber cinereum the pendular movements of the intestinal loops were sometimes slightly increased, but the rhythmic segmentation and peristalsis, the tonicity of the muscular wall and the state of the blood vessels remained unaffected. However, administration of larger amounts of strychnine (up to 0.20 mg. per kilogram) was always followed by abolition of motility and increased tonicity and blanching of the gut whether or not other sympathetic responses were concurrently elicited. A second injection of strychnine from 30 to 45 mins. after the effects of the first had worn off produced reactions in the gut similar to those induced by the initial injection.

When the toxic effects of large or repeated injections of strychnine began to appear (gradually falling blood pressure, disturbed respirations and convulsions), the intestine usually became motionless, spastic and cyanotic. In several animals, just before fatal respiratory paralysis supervened, the gut showed a vigorous burst of peristaltic and pendular movements despite the presence of marked spasticity and cyanosis.

*Changes in threshold.* Electrical stimulation of the right side of the tuber cinereum following the local injection of 0.07 to 0.08 mg. per kilogram of strychnine sulphate revealed inconsistently lowered thresholds for the intestinal motor responses. Similarly, depressant effects on the gut associated with emotional mimetic responses could usually be elicited with currents weaker than those necessary before the injection of the strychnine salt. When stronger stimuli were applied to the tuber, especially after large or repeated injections of strychnine, transient convulsions were usually induced and always foreshadowed ultimate respiratory failure. During this period the gut gradually became motionless, spastic and cyanotic, while the thresholds mounted rapidly until practically all responses to hypothalamic stimulation were abolished a few minutes before death.

#### *Recovery preparations*

A total of 23 fluoroscopic observations were made upon the 6 animals in this series. In 15 of these the hypothalamus was stimulated with currents which were too weak (0.05 to 2.0 volts AC) to cause overt emotional mimetic responses; that is, reactions other than those in the alimentary tract consisted

\* *Control Injections:* As shown in previous experiments (see reference in first footnote p. 350), the intradiencephalic injection of normal saline or Ringer's solution in amounts up to 0.2 cc. produces no observable effects and exerts no influence on the thresholds of electrical excitability if the injections are made at a rate of less than 0.1 cc. per min. When small amounts of India ink are added to the solution, the ink granules appear in minute tracts about the needle and, to a variable extent, in the third ventricle.

only in a slight restlessness and some increase in the rate of respiration. Nevertheless, in 11 of these 15 experiments segmentation and peristalsis in the small intestine were either initiated or definitely augmented and in one of the animals marked pendular movements were also induced. The intestinal responses appeared in from 5 to 15 secs. after the beginning of the stimulus and persisted for as much as 30 secs. after its cessation. In 2 of the animals in this series and in a number of others reported in previous communications,† retching and vomiting were observed during stimulation of the hypothalamus with weak or moderate currents. Of the other 4 experiments in which weak currents were used, 2 showed no change in the existing motility of the gut and in 2 the activity was found to be diminished. For the most part the entire small intestine appeared to respond as a unit.

In the remaining 8 experiments, strengths of current sufficient to induce widespread vegetative and emotional mimetic responses (2.0 to 6.0 volts AC) were employed. The general reactions then consisted in dilatation of the pupils, piloerection, extrusion of the claws, marked restlessness, hissing, growling and finally, fairly well directed clawing, fighting or running movements.\* During these responses and from 5 to 60 secs. thereafter the motility of the small intestine was diminished or abolished; further, the degree and persistence of the intestinal inhibition appeared to correspond directly with the vigor of the emotional mimetic effects produced by the hypothalamic stimulation. Similarly, in 2 animals which became markedly disturbed by accidental shocks from static charges on the fluoroscopic apparatus, the intestinal tract, as viewed fluoroscopically, became markedly atonic. In these animals, moreover, hypothalamic stimulation with weak currents was without effect until they had become quiet and spontaneous intestinal motility had returned, at which time typical augmentation of activity was obtained.

*Effect of strychnine in recovery preparations.* Injections of from 0.07 to 0.08 mg. per kilogram of strychnine sulphate into the diencephalon caused little or no change in the rate of segmentation and peristalsis of the intestine if the other sympathetic effects of the injection were mild. However, when the vegetative and emotional mimetic effects were marked, intestinal motility was uniformly found to be depressed. Stimulation of the hypothalamus following its injection with strychnine in recovery preparations revealed fairly consistently diminished thresholds for both the enteromotor and general emotional mimetic responses.

## DISCUSSION

In 1932 Beattie<sup>1</sup> demonstrated that electrical stimulation of the tuber cinereum in an anesthetized cat gave rise to vagal impulses which induced increased peristalsis and secretion in the animal's stomach. Beattie also

† MASSERMAN, J. H.: The effects of strychnine on the functions of the hypothalamus in emotional expression. *J. Pharmacol.* In press. MASSERMAN, J. H.: The effects of pentamethylenetetrazol (metrazol) on the hypothalamus. *Arch. Neurol. Psychiat., Chicago.* In press.

\* See references in first footnote p. 350.

anastomosed the central stump of one of the vagi with the peripheral end of the homolateral phrenic nerve and found that stimulation of the tuber 180 days after operation caused contraction of the diaphragm. Beattie and Sheehan<sup>2</sup> later reported that stimulation of the tuber cinereum raised the intragastric pressure independently of the peristaltic activity and that stimulation of the caudal portions of the hypothalamus diminished the intragastric pressure slightly and abolished gastric motility. Cushing<sup>3</sup> observed that marked hypervagotonic effects upon gastric motility followed injections of pituitrin and pilocarpine into the lateral ventricle in 3 of his patients, and regarded these reactions as evidence for a parasympathetic center in the interbrain. Finally, Kabat, Anson, Magoun and Ranson<sup>4</sup> fluoroscoped recovery preparations of cats and reported that inhibition of gastro-intestinal tonus and cessation of peristalsis occurred when structures in and about the hypothalamus were stimulated with currents sufficiently strong to induce marked emotional mimetic behavior and other evidences of widespread sympathetic discharge. These findings are in accord with our observations in experiments with these strengths of stimuli; however, we found in addition that weaker currents almost as uniformly increased intestinal motility, although the difference between motor and inhibitory effects was, in several of our experiments, as small as one volt.

#### SUMMARY

The effects of electrical stimulation of the hypothalamus and of the injection of strychnine into the diencephalon upon the motility and blood supply of the small intestine were examined by direct inspection in cats anesthetized with ether and by fluoroscopy in recovery preparations. Observations in 14 animals led to the following conclusions:

1. Stimulation of the anterior portion of the hypothalamus with currents too weak to induce typical emotional mimetic responses in an anesthetized animal causes marked pendular movements of loops of small intestine and, less consistently, segmentation and peristalsis of the gut. In some animals these stimuli cause the small vessels in the external intestinal wall to constrict or dilate slightly, but more frequently no change in vasotonicity can be observed. In the recovery preparations segmentation and peristalsis are induced or augmented more consistently than are the pendular movements.

2. Enteromotor effects are also obtained when the dorsal portion of the supramammillary decussation and the mammillary bodies are stimulated.

3. Inhibition of intestinal motility is induced by the application of strong electrical stimuli anywhere in the hypothalamus and of weak stimuli in the suprachiasmatic region or in the ventral portion of the supramammillary decussation. In stimulation of the hypothalamus the degree of intestinal inhibition corresponds to the intensity of the other autonomic and emotional mimetic responses elicited by the stimulus.

4. Injections of from 0.07 to 0.08 mg. per kilogram of strychnine sulphate into the diencephalon in cats causes either no change in intestinal activity or a slight accentuation in the intestinal movements. However, the injection



of larger amounts of strychnine into the diencephalon is consistently followed by spasticity, diminished motility and blanching of the small intestine.

5. Electrical stimulation of the hypothalamus after its injection with strychnine reveals inconsistently lowered thresholds for the diencephalic enteromotor reactions, the degree of intestinal inhibition in general corresponding to the degree of facilitation of the other vegetative and emotional mimetic responses of the animal to hypothalamic stimulation.

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# ON THE RELATIONSHIP BETWEEN CHOLINE ESTERASE AND THE DEVELOPMENT OF BEHAVIOR IN AMPHIBIA

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## INTRODUCTION

THE DESTRUCTION of acetylcholine by the enzyme choline esterase is thought to account for the short duration of the effect of a nerve stimulus (Dale, 1936). It has been shown that acetylcholine is liberated sometime after a motor nerve to striated muscle is stimulated (Dale, Feldberg and Vogt, 1936); and the amount of choline esterase present in the superior cervical ganglion is sufficient to accomplish the destruction of the acetylcholine liberated, presumably within the refractory period of that ganglion (Glick, 1938). The inactivation of choline esterase by eserine is well known (Gaddum, 1935). The behavior of amphibian embryos poisoned with eserine during the swimming stage is characterized by a gradual paralysis of the skeletal musculature, by a gradual loss of irritability to mechanical stimulation and by the development of contracture. A similar paralysis and contracture have been observed in amphibian embryos in the early swimming stage after they had been made to swim continuously for a few minutes by repeated mechanical stimulation. Therefore, it would seem that the slow relaxation of young amphibian embryos in the flexure, "U," and coil stages, and their quick fatigue through the early swimming stage\* might be related to some developmental condition in the embryos affecting the relations between choline esterase and its substrate, acetylcholine.

This is somewhat different from the explanation offered by McCouch (Coghill, 1929, p. 14). He suggested three factors which might act to prolong the coil reflex in *Amblystoma*: (i) The "early stage of development of the muscle and neurones," (ii) opposition to the movement by the "tonic contraction of muscles on the side of the exteroceptive stimulus," (iii) "the resulting increased tension in the muscles of the convex side may set up proprioceptive stimuli which accentuate and prolong the coil reflex." The first factor pertains to the differentiation of the tissues, and is related to the object of the present study. The second factor might be related to the low esterase content of this stage. The third factor, being based on the idea that proprioceptive stimuli may initiate muscular activity, is contrary to the report by Kato (1934) that proprioceptive fibers when stimulated give no response. That this finding may

\* Descriptions of these physiological stages are found in the publications of Coghill, 1929; Herrick, 1937; and Youngstrom, 1938.

hold also for the proprioceptive endings of the Rohon-Beard cells is, of course, open to question.

Assuming that acetylcholine is liberated by the nervous system of these embryos, its effect on the somites would be influenced by at least three fac-

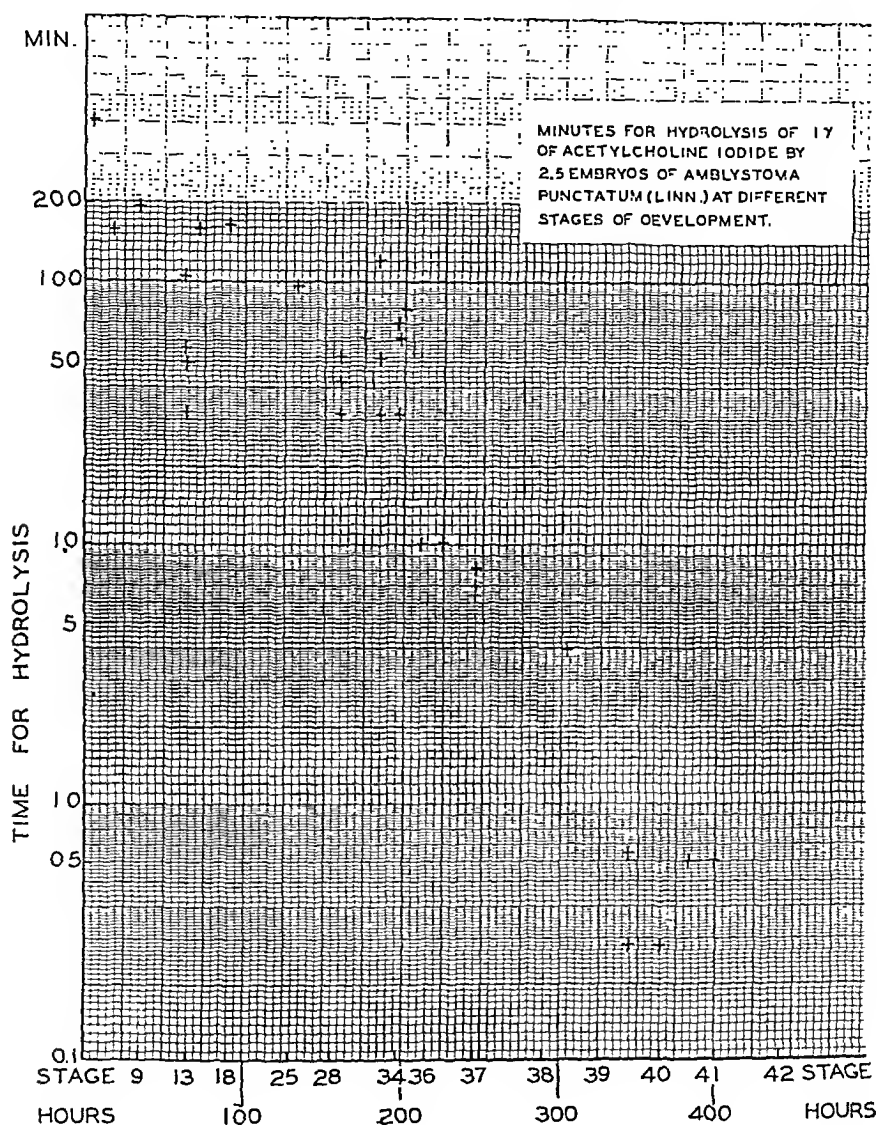


FIG. 1

tors: (i) The gradually decreasing concentration of salts in the embryo during the period of development (Schaper, 1902; Dempster, 1933; Youngstrom, 1938) might help to make the developing somites more sensitive to acetylcholine.\* (ii) The avascular condition of the nervous and muscular tissues

\* Clark (1927) has shown that a reduction of potassium in Ringer's solution increased the sensitivity of the heart to acetylcholine while an increase of potassium or calcium reduced this sensitivity.

until the swimming stage (Coghill and Moore, 1924) would allow the products of the choline esterase hydrolysis to accumulate locally. (iii) The amount of choline esterase present would influence the rate of destruction of the acetylcholine. If the amount of choline esterase were relatively small, acetylcholine might accumulate in the muscles. In this event one would expect

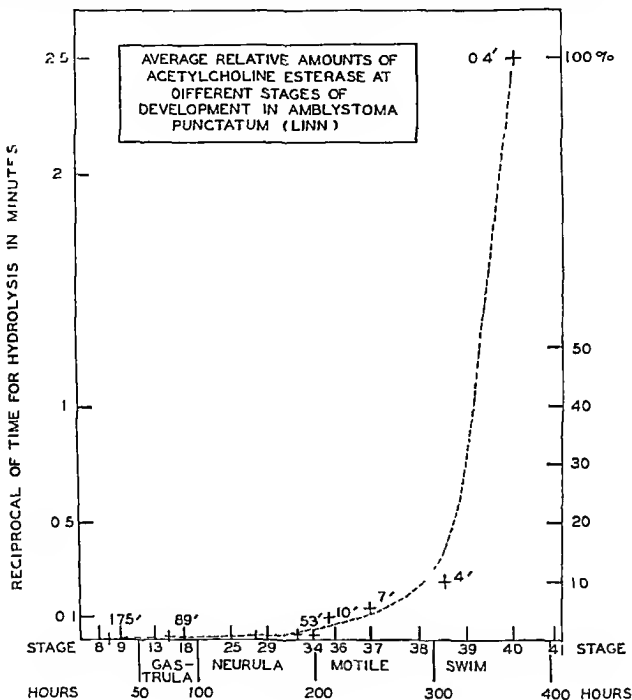


FIG. 2

from the work of Brown (1937) that the somites of both sides of the embryo would be in a state of partial tetanus. The developing behavior of these embryos is in harmony with this idea. To determine the amount of choline esterase present during the period of developing motility is the object of this study.

#### MATERIAL AND METHODS

Embryos of *Amblystoma punctatum*, *Bufo terrestris*, and *Rana sphenoccephala* were used in these experiments. A definite number of embryos were selected according to their degree of morphological development\*; and their type of reaction to mechanical stimuli.

\* The *Amblystoma* embryos were staged according to Harrison's figures for the normal development of this form.

They were then ground in a mortar and made up to a standard volume with water and a limited amount of phosphate buffer pH 7.61. A definite amount of this suspension was added to a known amount of acetylcholine iodide solution, and samples of this mixture were tested at frequent intervals on guinea pig ileum after the method of Bernheim and Bernheim (1936). Failure of the gut to respond to the standardized test samples indicated the destruction of a definite amount of acetylcholine iodide. The preparations were sensitive to acetylcholine iodide diluted to 1 part in 7,500,000. This is a greater sensitivity

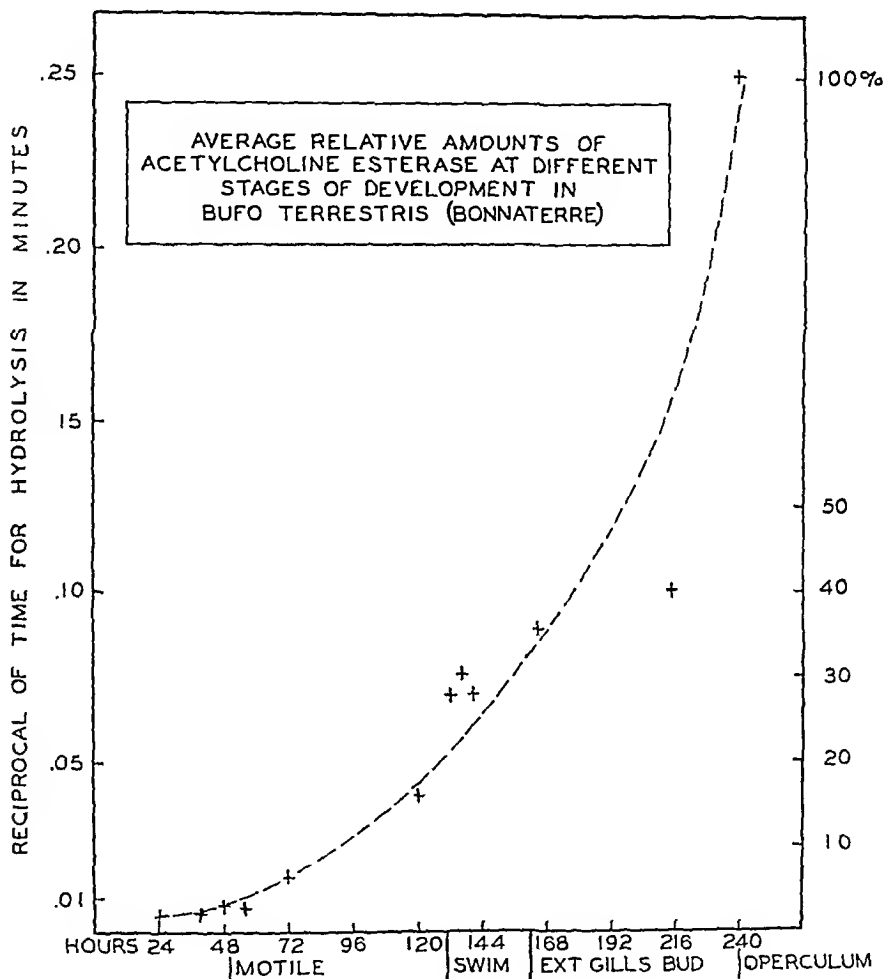


FIG. 3

than was ascribed to this method by the Bernheims, because the use of a smaller vessel made it possible to suspend the guinea pig ileum in only 15 cc. of fluid.

The total amount of enzyme present was found to be so small that no attempt was made to extract it. The effect on guinea pig ileum of the ground embryo suspension itself as well as that of the alkaline buffer, was controlled by using test samples which contained less than threshold amounts of these substances.

The temperature during the time the enzyme and substrate were allowed to react was held constant for each series. The determinations on *Amblystoma punctatum* were done at 37°C.; those on *Bufo terrestris* and *Rana sphenocephala*, were done at 25°C.

## RESULTS

The amount of choline esterase present at different stages of development in the three species studied is presented graphically in Figs. 1 to 4. Fig. 1 is plotted on semi-log paper to show the distribution of the data. Fig. 2 is constructed from the same data to show directly the relative amount of enzyme. In Fig. 1 each + sign represents one determination, while in Figs. 2, 3 and 4

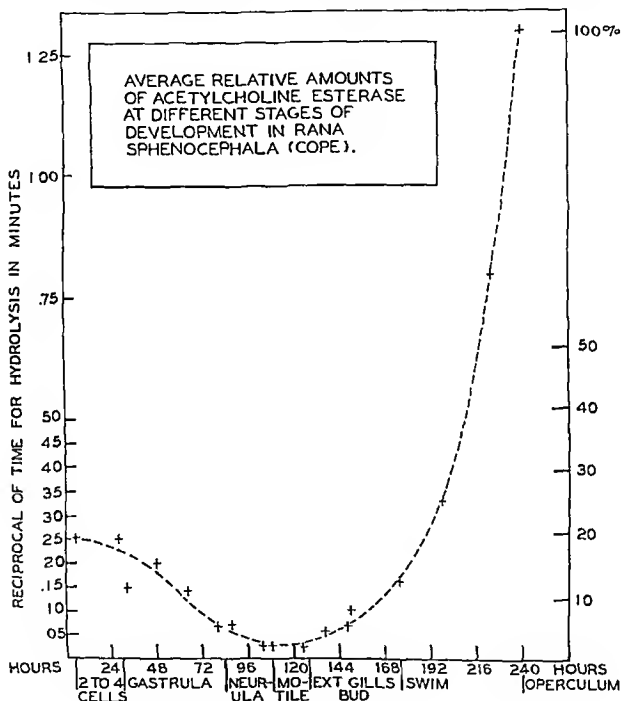


FIG. 4

each + represents the average of several determinations. The ordinate scale represents time in Fig. 1. In Figs. 2, 3 and 4 it represents the reciprocal of the times for hydrolysis of 1 gamma of acetylcholine iodide by 2.5 *Amblystoma* embryos, by 1.25 toad embryos and by 5 frog embryos, respectively. The percentage scale arbitrarily represents the highest value on each graph as 100 per cent.

The difference in the ordinate scale as observed in Figs. 2, 3 and 4 may

be explained largely on the basis of the difference in dry weight of the three species. The average dry weight of an individual embryo in the early swimming stage is 2.2 mg., 0.5 mg., and 1.3 mg. for *Amblystoma punctatum*, *Bufo terrestris* and *Rana sphenoccephala*, respectively. The increase in the amount of the enzyme would be relatively greater if it were expressed in terms of dry weight instead of the number of embryos, because the dry weight is decreasing slightly during this phase of development. Although there is considerable species difference in the character of these curves, all show a significant increase during the period of developing motility. From the beginning of motility to the early swimming stage there is a 13 fold, 5 fold and 5 fold increase of the choline esterase in *Amblystoma punctatum*, *Bufo terrestris*, and *Rana sphenoccephala*, respectively. The enzyme, moreover, is present before the nervous system appears. The amount is then very small in *Amblystoma punctatum* and in *Bufo terrestris*, but quite considerable in *Rana sphenoccephala*. In the last named species it is as abundant in the 2 and 4 cell stage as in the early swimming stage.

#### SUMMARY AND CONCLUSIONS

The amount of choline esterase present during representative stages of development has been determined for 3 species of amphibian embryos. A significant increase occurred in all 3 species during the period of developing motility. These data do not bear directly on the explanation of the prolonged character of the coil reaction offered by McCouch, but should contribute to a better understanding of the slow relaxation and early fatigue of young amphibian embryos. It seems that a satisfactory explanation of developing behavior must consider neurohumoral factors of nerve physiology, as well as the developing patterns of neuroanatomy.

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# SENSORIMOTOR CORTEX, NUCLEUS CAUDATUS AND THALAMUS OPTICUS\*

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## INTRODUCTION

SEVERAL anatomists (Cajal,<sup>1</sup> Marinesco,<sup>10</sup> Minkowski,<sup>11</sup> Kariya,<sup>8</sup> Hirasawa and Kariya<sup>7</sup>) have described corticostriatal neurons, originating in the sensorimotor cortex. Nevertheless the present tendency in neuroanatomy and neurology is to ignore these findings and to maintain that the cerebral cortex does not directly influence the activity of the striatum, an opinion understandable in the absence of physiological evidence of a directed functional relation from cortex to striatum.

In this paper† direct experimental evidence for such a functional relation is presented. It will be shown: (i) that two specific areas of the sensorimotor cortex, namely the areas L.4-s and A.4-s‡ influence the activity of one of the constituent portions of the striatum, *viz.*, the nucleus caudatus, (ii) that these areas L.4-s and A.4-s via this nucleus influence the activity of the thalamus, and (iii) that these areas via nucleus caudatus and thalamus influence the activity of two other areas, *viz.*, the leg-and arm-portions of area 4 (L.4 and A.4) of the sensorimotor cortex. In other words, in this paper will be demonstrated by physiological methods the existence and operation of the following one-way system:

*Areas L.4-s and A.4-s→nucleus caudatus→thalamus opticus→areas L.4 and A.4*

This has been done by combining recording of electrical activity, local strychninization and operative lesions of the nervous structures involved. The connection between the caudate nucleus and thalamus has been indicated by a dotted arrow, because the course of the neurons establishing this connection is as yet uncertain (see discussion, p. 376).

## METHODS

All experiments were performed on monkeys (*Macaca mulatta*) fully anesthetized with Dial§ (0.45 cc. per kilogram bodyweight, half of the dose given intraperitoneally, half intramuscularly). In some experiments curarization was used.

In these experiments the method of local strychninization was combined, as in previous investigations<sup>2,3</sup> with that of recording the electrical activity of various levels of the brain. The local strychninizations of the caudate nucleus were performed by injecting minute quantities of a 3 per cent strychnine solution (0.3–1.0 cmm. = 10–30γ of strychnine) by

\* The expenses of this investigation were defrayed by a grant from the Fluid Research Funds of Yale University, School of Medicine.

† A preliminary report of this investigation was presented before the annual meeting of the American Neurological Association at Atlantic City on May 3, 1938.

‡ For the designation of the various cortical areas see Dusser de Barenne and McCulloch.<sup>2</sup>

§ The Dial was kindly put at our disposal by the Ciba Company.

means of the micro-injection method developed by Dusser de Barenne and Sager.<sup>46</sup> The electrical activity from the various portions of the sensorimotor cortex (electrocorticogram: ECG) was recorded simultaneously with bipolar Ag-AgCl<sub>2</sub> electrodes through AC-amplifiers and a Westinghouse four-element oscillograph; the electrograms from the subcortical structures, the caudate nucleus and the various thalamic nuclei, were taken with concentric needle-electrodes,<sup>3</sup> in which the inner insulated electrode protruded 1.5 mm. beyond the outer one, the hypodermic needle proper. The animals and the electrodes were placed on a table in a large Faraday-cage, so that the recordings of the electrical activity were undisturbed by extraneous electrical fields.



FIG. 1. "Knife," a little piece of thin flat steel sharpened at the edge, on needle-holder and stand for placing small lesions in subcortical structures. As a holder for the needle with the knife serves a pinvice, which can be rotated around its length-axis on a closely fitting pin mounted rigidly in the micro-injection apparatus. Thus a small lesion can be made in the particular subcortical structure. The needle is withdrawn in the same vertical position in which it was introduced; thus the smallest possible "track" outside the desired subcortical structure is obtained.

In a number of the experiments localized lesions were made in various subcortical structures, *viz.*, the optic thalamus, the caudate nucleus and other portions of the striatum. The apparatus was a little "knife" soldered to the end of an ordinary sewingneedle and mounted on a needle-holder, instead of the tuberculin-syringe, in a microinjection apparatus of Dusser de Barenne and Sager (see Fig. 1). This "knife" was introduced into the desired subcortical structure in a vertical plane, then the needle-holder was turned 360° around its length-axis; thus the knife produced a sharply localized, olive-shaped lesion, the shape and size of which is determined by the shape and size of the "knife." The length of such a lesion can be increased by screwing the "knife" back by the micrometer-screw of the apparatus over a few millimeters and then repeating the rotation around the length-axis of the needle. Finally the "knife" was withdrawn from the brain by screwing it back in its original position in the vertical plane.

## RESULTS

As shown previously<sup>2</sup> the local strychninization of area A.4-s or L.4-s results in a temporary suppression of the electrical activity of the areas A.4 and L.4. It was stated there that this suppression does not depend upon interareal connections, but occurs via one or more subcortical structures. This statement was based upon the following two groups of experiments.

- A. (i). An incision between area A.4-s and area A.4, 10 to 12 mm. deep, does not prevent this suppression (see Fig. 2).

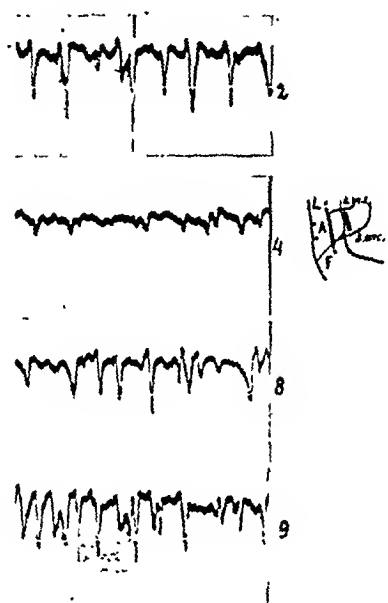


FIG. 2. October 18, 1937. Macaque. Dial-narcosis. ECG of area A.4 (:) before (record 2) and after (records 4, 8 and 9) local strychninization of area A.4-s. Before the records were taken a deep cut ( $\frac{x}{x}$ ), 9½ mm. deep, was made between A.4 and A.4-s. Record 4 taken two minutes, record 8 nine minutes and record 9 thirteen minutes after the local strychninization of A.4-s. Note suppression in ECG of record 4 with gradual return to normal in records 8 and 9. Diagram: L, A, F=leg- arm- and face subdivisions of precentral sensorimotor cortex.: =position of electrodes on A.4. S. pr. S=Sulcus precentralis superior, S. arc. =S. arcuatus.

- (ii). The undercutting of area A.4-s does prevent the suppression (see Fig. 3).

These two experiments prove that this suppression involves connections from area 4-s to some subcortical structure. The following experimental evidence points to the *nucleus caudatus*.

- B. (i). The nucleus caudatus is "fired" by local strychninization of area 4-s, either L.4-s or A.4-s (see Fig. 4).  
 (ii). The nucleus caudatus is not "fired" by local strychninization of areas L.4, A.4, L.6a or A.6a (see Fig. 5). The site of strychn-

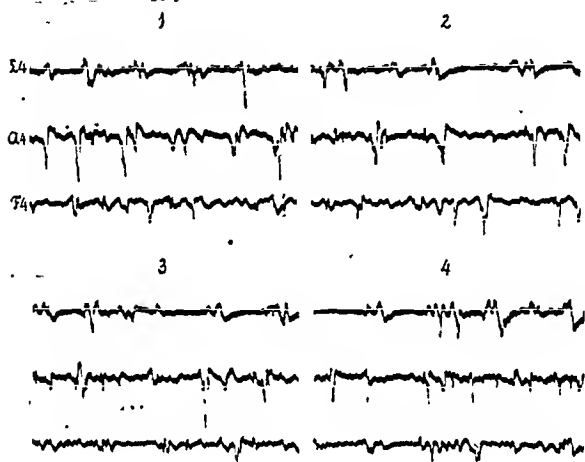


FIG. 3. October 20, 1937. Macaque. Dial-narcosis. ECGs from L4, A4 and F4. All records taken after undercutting of A4-s and L4-s. Record 1 taken before local strychninization of A4-s, records 2, 3 and 4 after this strychninization. Note absence of suppression in ECGs of A4 and L4.



FIG. 4. February 14, 1938. Macaque. Dial-narcosis. Local strychninization of A4-s resulting in strychnine-spikes in electrogram of nucleus caudatus. Record 1 before, record 2 five minutes after this strychninization, record 3 fifteen minutes later. The spiking in the ECG of A4 (record 2) is due to the fact that the strychninization slightly encroached upon A4.

ninization in the caudate nucleus in the particular experiment from which Figs. 4 and 5 are taken is shown in Fig. 6.

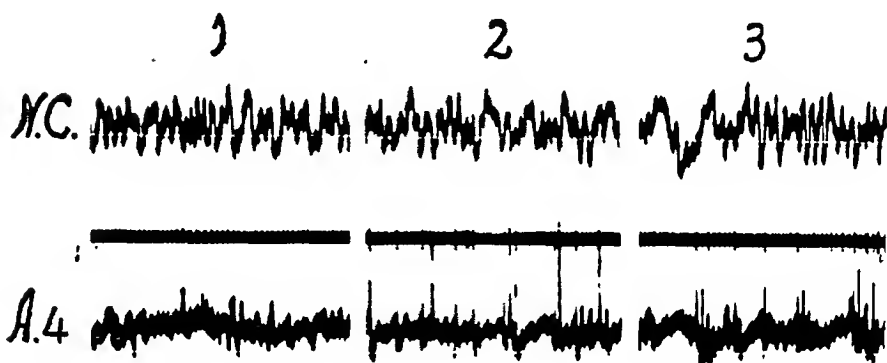


FIG. 5. Same animal as of Fig. 4. Record 1 electrograms of nucleus caudatus and A.4 before strychninization. Record 2 same after local strychninization of A.4: spiking in ECG of A.4, not in electrogram of N. C. Record 3 same after local strychninization of A.6a: spiking in ECG of A.4, no "firing" of nucleus caudatus.

The interpretation of these findings consistent with the conclusions from previous observations<sup>2</sup> is that the strychnine applied to area 4-s has acted upon perikarya of neurons with axons or axonal collaterals ending in and thus "firing" the caudate nucleus, and that of the areas mentioned above area 4-s only is directly connected with the caudate nucleus.

Further evidence implicating the caudate nucleus is found in the following groups of experiments.

- C. (i). An experimental lesion in the occipital portion of the caput nuclei caudati is immediately followed by a marked increase of electrical activity of A.4 and L.4 persisting for half an hour to two hours (see Fig. 7b).



FIG. 6. Fig. 6 shows track of concentric needle-electrodes in nucleus caudatus of experiment of Figs. 4 and 5.

- (ii). Subsequently, local strychninization of A.4-s or L.4-s fails to suppress the activity of A.4 and L.4 (Compare Fig. 7a (before) and 7c (after lesion in nucl. caud.))

The lesion made in the nucleus caudatus, which gave rise to the "release" of area A.4 pictured in Fig. 7b and prevented the suppression of area A.4 recorded in Fig. 7a and 7c, is shown in Fig. 8.

- (iii). Local strychninization of the caudate nucleus results in a typical temporary suppression in areas A.4 and L.4, similar to that appearing after local strychninization of area A.4-s or area L.4-s (see Fig. 9). Comparing the ECG of A.4 in Fig. 9 (1) with that in Fig. 9 (3), it will be seen that the activity in the latter is definitely enhanced. This is a consistent finding, to be expected inasmuch as the introduction of a needle into the caudate nucleus inevitably produces a lesion. Apparently the suppression of the activity of area A.4 due to the hyperactivity of the locally strychninized caudate nucleus is sufficient to overshadow temporarily the "release" of this area by such a small destructive lesion. The site of strychninization in the caudate nucleus in the particular experiment from which Fig. 9 is taken is given in Fig. 10.

One of the few points upon which neuroanatomists unanimously agree is that in the caudate nucleus arise no corticopetal neurons, *i.e.*, they all deny the existence of caudatocortical axons, a conclusion substantiated by our repeated failures to find "firing" of any portion of the sensorimotor cortex by local strychninization of the caudate nucleus.

The experiments presented here show conclusively that the caudate nucleus affects the activity of areas A.4 and L.4. There must be, therefore, some indirect connection between this nucleus and these areas of the sensorimotor cortex. *This requires a subcortical structure which 1. is affected by the nucleus caudatus and 2. itself, in turn, affects the activity of A.4 and L.4 of the sensorimotor cortex.* All physiological and anatomical evidence points to the *optic thalamus*.

- D. (i). Therefore, in several experiments the electrical activity of some of the arm- and leg-nuclei of the thalamus,<sup>3</sup> *i.e.*, the electrothalamograms (ETG) of these nuclei, were recorded simultaneously with the ECGs of areas A.4 and L.4, before and after local strychninization of the caudate nucleus. It was found that such strychninization temporarily suppresses the activity of the thalamus as well as that of areas A.4 and L.4 (see Fig. 11). In Fig. 12 is shown the position of the thalamic electrodes and the site of strychninization in the caudate nucleus in the particular experiment of Fig. 11. Thus the thalamus fulfils the first requirement mentioned above.

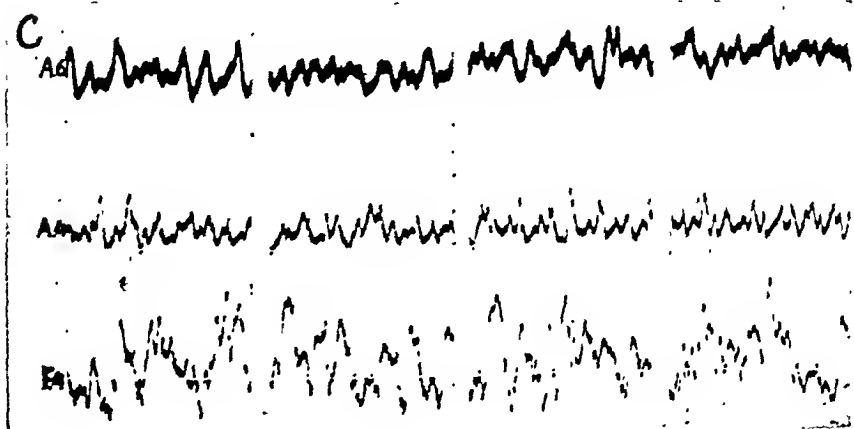
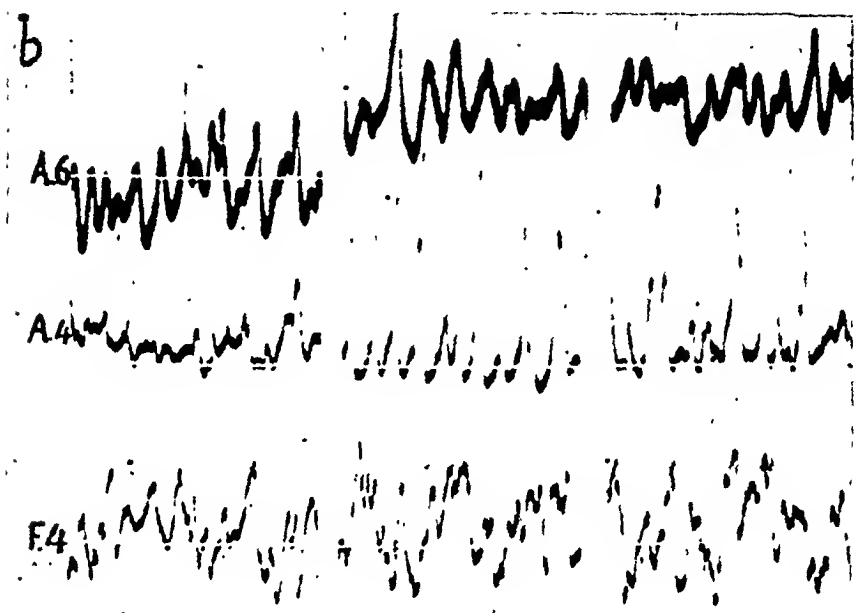
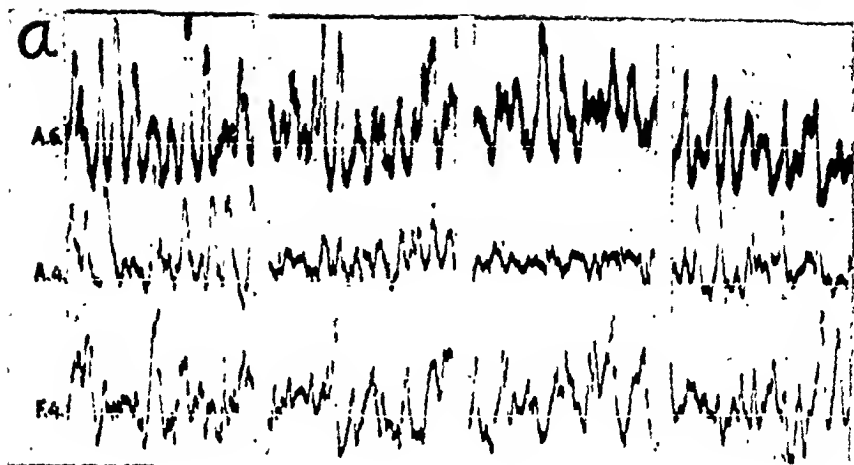


FIG. 7. (For legend see opposite page.)

- (ii). With respect to the second requirement it has been stated in a previous paper<sup>3</sup> that strychninization of the thalamus results in "firing" of the sensorimotor cortex. Experiments of this kind show that, as one would expect, the thalamus affects the

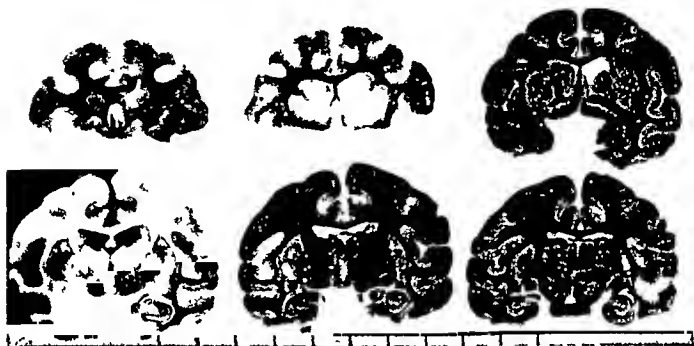


FIG. 8. This figure shows lesion of nucleus caudatus in experiment of Fig. 7.

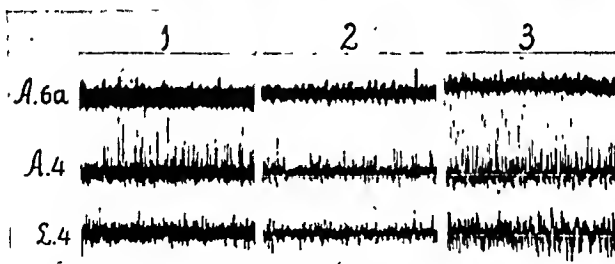


FIG. 7. Macaque. Dial narcosis. Simultaneous ECGs of A.6, A.4, F.4. In Fig. *a* typical temporary suppression of A.4 upon local strychninization of A.4-s. In Fig. *b* "release" of A.4 after acute lesion in nucleus caudatus; record 1 of *b* before lesion. In Fig. *c* absence of suppression (after "release" has subsided several hours after lesion) upon local strychninization of A.4-s.

activity of the cortex, but not that cortical activity depends upon thalamic activity. However, this can be shown by undercutting the sensorimotor cortex, thus destroying thalamocor-





FIG. 10. Site of strychninization in caudate nucleus in experiment of Fig. 9.

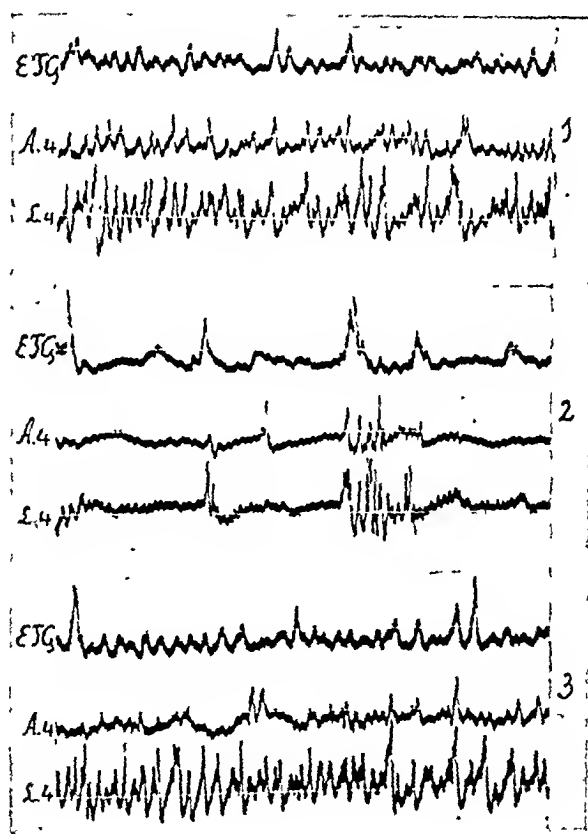


FIG. 11. Macaque. Dial-narcosis. ETG of a leg-nucleus of the thalamus and ECG of A.4 and L.4. Record 1 "normal"; in record 2, after local strychninization of caudate nucleus, suppression in ETG and ECGs. In record 3 return to "normal" of all electrograms.

tical connections. The simultaneous severance of the corticothalamic neurons is obviously of no importance here. In the acute experiment such an undercut cortex is "silent," i.e., its electrical activity is abolished, though its threshold for cortical after-discharge to electrical stimulation, if altered at all, is slightly lowered. In the chronic experiment, even with undercutting of a portion of the sensorimotor cortex only, for



FIG. 12. This figure shows the position of the concentric needle-electrodes in nucleus *lbn* (leg-nucleus) of the thalamus of the right hemisphere and the site of strychninization in the right caudate nucleus in experiment of Fig. 11. The needle-electrodes were introduced into the right thalamus through the left hemisphere so as not to damage the right corticothalamic and thalamocortical connections.

instance of the precentral arm-area, though the electrical activity has returned to some extent, the ECG, even after a survival period of 2.5 years, is highly abnormal. *These observations prove that the ECG normally depends directly on thalamic impulses impinging upon the cortex.*

The same can be shown by acute experimental lesions in the sensory nuclei of the thalamus. These also result in a marked diminution of the electrical activity in the corresponding subdivisions of the sensorimotor cortex. Yet, even the residual cortical activity of areas A.4 and L.4 depending upon the remnants of the sensory nuclei of the thalamus still shows a trace of suppression upon local strychninization of the caudate nucleus (see Figs. 13 and 14).

Taken together, these results show that the thalamus fulfills both of the above mentioned requirements for a subcortical structure linking the caudate nucleus with areas A.4 and L.4 of the sensorimotor cortex.

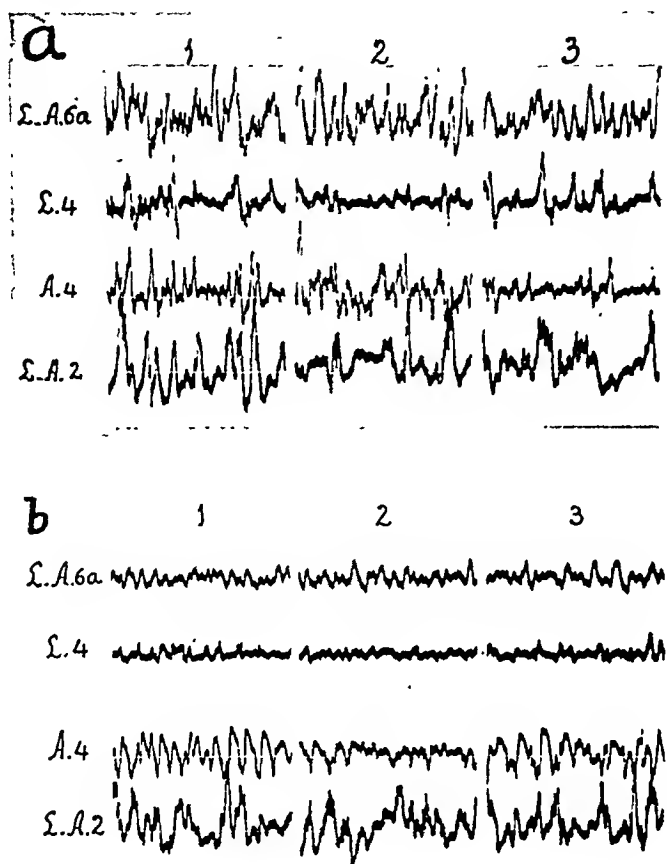


FIG. 13. March 18, 1938. Macaque. Dial-narcosis. Fig. 13 *a* shows ECGs of various cortical areas before and after local strychninization of A.4-s. Note suppression in ECG of L.4 in 2 and in ECG of A.4 in 3. The records of Fig. 13 *b* were taken almost two hours after a lesion of the leg-nuclei of the thalamus. Record 1 before, records 2 and 3 after local strychninization of A.4-s. Note the typical suppression in ECG of A.4 in record 2 with return to normal in record 3. Note also that even the reduced activity of L.4, due to the lesion of the leg nuclei, is temporarily somewhat suppressed (record 2).

### DISCUSSION

The experiments reported in this paper are concerned only with the pre-central portions of the arm- and leg- subdivisions of the sensorimotor cortex, the corresponding sensory nuclei of the thalamus and the posterior portion of the caput and the anterior portion of the cauda of the nucleus caudatus. Neither strychninization nor lesion of these structures has appreciably altered the electrical activity of area F.4. These statements constitute important re-

strictions because it has been found that the functional organization in the precentral face-subdivision of the sensorimotor cortex is so different from that in the precentral arm- and leg-subdivisions that the subject must be dealt with in a separate paper.

As mentioned previously<sup>2</sup> our areas A.4-s and L.4-s are identical with that portion of the "strip" of Marion Hines<sup>6</sup> which lies on the outer surface of the arm- and leg-subdivisions of the sensorimotor cortex. The striking analogy of her finding, namely abolition of existing motor activity on electrical stimulation of the "strip," with our suppression, the abolition of an existing elec-

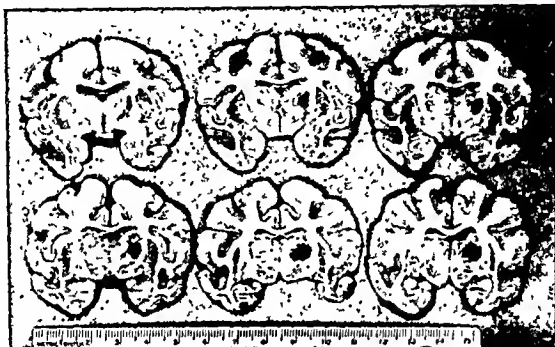


FIG. 14. Lesion of some of the leg-nuclei of the thalamus in experiment of Fig. 13. There is a slight haemorrhage also in nucleus va (arm nucleus) in middle picture of bottom row. In the first picture the slit made by the introduction of the "knife" in the vertical position is seen; the oval lesions in the subsequent pictures are made by the rotation of the "knife" around its length-axis.

trical activity of areas A.4 and L.4 upon local strychninization of the "strip" (A.4-s and L.4-s), has been mentioned there too. Now another analogy has become apparent. We have not indeed destroyed the "strip," which operation in the hands of Marion Hines resulted in spasticity for some days, but we have destroyed a large portion of the nucleus caudatus (shown here to be a necessary link in the pathway from areas 4-s to the thalamus and so to areas A.4 and L.4 of the cortex), which resulted in a release of these areas for a matter of hours. Marion Hines has not shown what pathways emanating from her strip are involved in the production of the spasticity. Therefore, one cannot without more ado identify the subcortical structures involved in the production of this spasticity with those responsible for the "release" of areas A.4 and L.4. If these structures are significantly different, the durations of the disturbances might be different for that reason alone. Apart from this, our lesions in the caudate nucleus were far from complete destructions and the duration of our release depended upon the size of the lesion. Just so the

duration of spasticity varied with the extent of Hines' lesions. Finally it should be pointed out that our animals were fully anesthetized throughout the experiment, whereas Hines' animals were not under narcosis. These latter considerations indicate that the discrepancy in duration of the two phenomena is not a serious objection against the stated analogy. The fundamental difference is of course that Marion Hines investigated disturbances *descending* to striped muscle, whereas our experiments upon suppression of areas A.4 and L.4 dealt with disturbances affecting thalamocortical activity, *i.e.*, *ascending* to the cerebral cortex.

In the introduction the linkage between the caudate nucleus and the thalamus was represented by a dotted arrow to indicate that its path is as yet undetermined. Neuroanatomy has not solved this problem. A few authors have described direct short caudatothalamic neurons; others have described longer caudatothalamic neurons running through the laminae medullares of putamen and globus pallidus, and still others—in fact the majority of neuroanatomists—deny the existence of both of these direct systems and acknowledge only indirect connections between the caudate nucleus and thalamus with a synaptic relay in the pallidum (see the synopsis by Kodama<sup>9</sup>). In this respect it is of interest that, although large lesions in the putamen do not cause "release" or prevent suppression of areas A.4 and L.4, one experiment in which such a lesion was extended into the pallidum did prevent suppression without causing release. By no such experiment can one distinguish between long direct caudatothalamic neurons and systems relayed in the pallidum. Yet this experiment does suggest that somehow impulses necessary for suppression pass through this region; it does not preclude the existence of or the necessity of activity in short direct caudatothalamic neurons.

That large lesions in the putamen neither cause release nor prevent suppression of areas A.4 and L.4 is entirely in harmony with the absence of any strychnine-spikes in the electrogram of the putamen upon local strychninization of areas A.4-s and L.4-s. These findings suffice to show that in spite of the anatomical homogeneity of the nucleus caudatus with the putamen, the latter is not a part of the system discussed in this paper.

From the observations reported here it is clear that the caudate nucleus "brakes" the activity of the thalamus and, via this structure, that of the areas A.4 and L.4 of the sensorimotor cortex. This is evidenced by the findings that a lesion in the caudate nucleus temporarily releases the activity of these cortical areas and that hyperactivity of this nucleus, induced by its local strychninization or by that of either area A.4-s or L.4-s of the sensorimotor cortex, suppresses the activity of areas A.4 and L.4 of this region of the cortex.

The experiments reported, therefore, constitute a demonstration *by physiological means* that the striatum, more particularly the caudate nucleus, does not function independently of the cerebral cortex. On the contrary; it has been shown here: (i) that specific areas (A.4-s and L.4-s) of the sensorimotor cortex directly influence, excite, or activate, the caudate nucleus, (ii) that the activity of this subcortical structure influences, or "brakes," albeit

indirectly via the optic thalamus, the activity of other equally specific areas (A.4 and L.4) of the same sensorimotor cortex.

# SUMMARY

1. The suppression of the electrical activity of A 4 and L 4 by local strychninization of A.4-s or L.4-s involves subcortical structures, namely, the nucleus caudatus and the thalamus opticus

2. The nucleus caudatus is "fired" by local strychninization of A.4-s or L 4-s, but not by that of A 4, L.4, A.6a or L 6a.

3. A lesion in the nucleus caudatus temporarily "releases" A 4 and L.4.

4. Strychninization of the nucleus caudatus produces a typical suppression of the electrical activity of thalamus and of A.4 and L 4.

5. The normal electrical activity of the sensorimotor cortex depends upon the influx of thalamocortical impulses.

6. The putamen is not involved in this system.

7. The pathway from nucleus caudatus to thalamus is as yet undetermined.

8. The functional one-way system described in this paper is constituted as follows.

A.4-s and L 4-s → nucleus caudatus → thalamus opticus → A.4 and L 4.

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# REFLEX DISCHARGE FROM THE SPINAL CORD OVER THE DORSAL ROOTS

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## INTRODUCTION

THE EXPERIMENTS described in this paper started from an observation made on the saphenous nerve of the cat. In order to send controlled volleys of impulses toward the spinal cord, the usual stimulating electrodes had been supplemented with lead electrodes, so that the content of fibers active in the nerve could be ascertained. It was observed that, in addition to the potentials arising directly from the stimulating electrodes, there appeared a large group of potentials resembling closely the reflex discharge that is seen in a mixed nerve in sequence to an afferent volley. Since it is known from the work of Heinbecker, O'Leary and Bishop (1933) and others that the saphenous nerve, apart from a fraction of the C fibers contributed by way of the grey rami, is made up exclusively of fibers of dorsal root origin, the possibility appeared to be at hand of obtaining new information about the discharges over the dorsal roots that have previously been described by Gotch and Horsley (1891) and by Matthews (1934).

A few preliminary experiments were performed to establish the validity of the observation and to orient further work. The following results were obtained:

1. Persistence of the discharge in the saphenous nerve, when the stimulating electrodes were transferred in turn to the homolateral tibial or peroneal nerve, showed that the discharge was of a reflex nature.

2. Discharges of the same type in dorsal roots connected only with the cord, when other roots or various peripheral nerves were stimulated, confirmed the involvement of these structures in the reflex.

3. That the potentials led from the saphenous nerve were not produced by movement of the preparation and were not artifacts derived from other nerves or from muscles was shown in a number of ways. (i) The discharge was large. It was clearly visible in a neurogram in which a maximal spike could be recorded. High amplification was not necessary and, therefore, the danger of picking up distant potentials was minimized. (ii) The impulses were readily recorded when a long stretch of nerve was freed from the body and the leads were placed near the cut ends of the nerve with the ground lead in the proximal position, the preparation otherwise being without connection with the ground. (iii) The potentials were still present when the preparation was curarized or when all motor nerves to the hind limbs had been severed. (iv) The reflex discharge was reversibly blocked by cocainization of the nerve central to the leads. (v) When the stimulating electrodes were placed at the end of the nerve and a diphasic lead was made proximal to them, the initial phase of

the discharge was in the direction opposite to that of the initial phase of the afferent volley, showing that the two sets of impulses were being conducted in opposite directions.

After satisfactory proofs had been obtained for the existence of the reflex, a series of experiments was designed with the end in view of learning the properties of the reflex.

#### METHODS

Nerves in good condition and at body temperature are subject to spontaneous firing if exposed to air and the impulses maintain the spinal cord in a continuously conditioned state, thereby reducing the reflex responses to experimentally induced afferent volleys. In order to obviate this difficulty two methods were employed. When velocities of conduction were of importance and the nerve had to be kept at body temperature, firing was prevented by keeping the nerve in 5 per cent CO<sub>2</sub> in oxygen, as described by Lehmann (1937). When velocities of conduction were not of special significance, it sufficed to allow the exposed portion of the nerve to become equilibrated to the temperatures of the laboratory (25°C.-30°C.), as at these

Decerebrated cats were used. Cases of dial narcosis were employed to exhibit any significant difference from similar experiments performed on decerebrated preparations.

For simultaneous leads the differential input circuit described by Toennies (1938) was employed. As between the several leads on a preparation, the disturbance at any given pair of leads due to potential differences between these leads and a grounded point of the preparation, or between these leads and any other pair of leads, is not more than one-thousandth part of the potential differences in question.

#### RESULTS

*Form of the reflex.* The reflex appears at a fixed interval after the stimulus producing the exciting afferent volley, the interval being determined by the sum of the conduction times in the nerve fibers involved in the afferent and efferent arms of the reflex and the central reflex time. In homolateral reflexes excited by strong volleys the action potential of the discharge, whether recorded in the roots or in the saphenous nerve, rises rapidly to a maximum. A peak is reached within 1-2 msec. (Figs. 1, 3, 8, and 11); then the potential declines along a curve which shows two or three secondary crests spaced 2.5-3.5 msec. apart (Fig. 1c, d, g, 3a, 7b, 8b).<sup>1</sup> The total duration of the discharge lasts 20-30 msec.

A typical picture of the reflex produced in the saphenous nerve when the saphenous nerve itself is stimulated is shown in Fig. 1. A portion of the nerve was exposed in the leg and placed on electrodes arranged as in the diagram in Fig. 1a. In this arrangement, the spike set up at the centrally placed stimulating electrodes is conducted to the end of the nerve and there recorded monophasically. It shows the fiber content of the volley which is set up by the same stimulus and conducted toward the central nervous system. About 8 msec. after the stimulus the reflex discharge begins to be recorded. It will be noted that after the first large discharge there is an additional, discrete, wave (Fig. 1c) composed of impulses conducted at a slower velocity. This wave,

<sup>1</sup> While this paper was in press, it was shown by additional experiments that the second and third crests are attributable to the repeated activity of fibers that responded during the first crest.



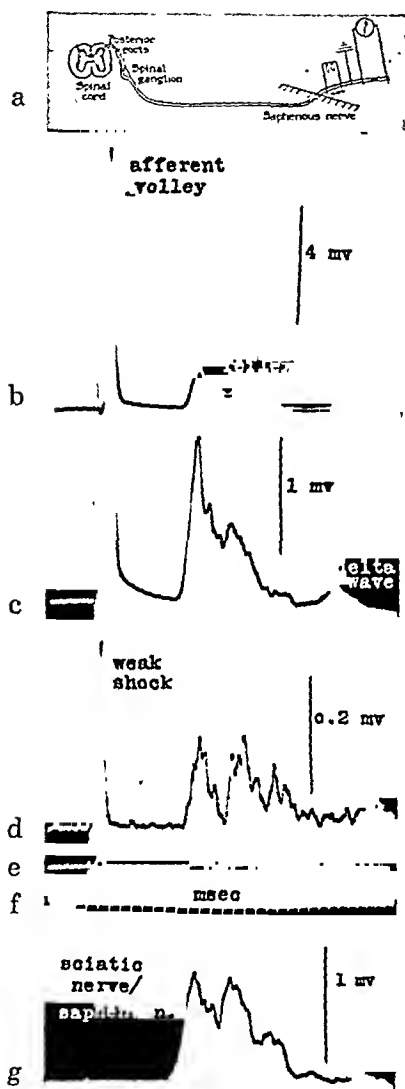


FIG. 1. Dorsal root reflex. Decerebrated cat. *a*, arrangement of electrodes: stimulus and lead on saphenous nerve. *b*, maximal stimulation of alpha fibers with reflex. *c*, same as *b*, but at  $4\times$  the amplification. *d*, weak shock with reflex following: amplification  $20\times$  that of record *b*. *e*, weak shock, recorded with same amplification as *b*. *f*, time 1 msec. each. *g*, stimulus on sciatic nerve, lead on saphenous nerve, amplification as for *c*, speed as for *f*.

which will be shown to be made up of action potentials in delta fibers, is typical of all saphenous to saphenous reflexes; but it is not seen in reflex discharges into the saphenous brought out by afferent volleys in other nerves.

When the reflex is contralateral, a different picture is obtained. The reflex is much smaller, and instead of starting with a burst of impulses, the discharge starts in a few fibers and builds up gradually to a maximum over a period varying between 6 and 20 msec., depending upon the conditions. In Fig. 2 a comparison is made between a homolateral and a contralateral saphenous to saphenous reflex in the same preparation; and in Fig. 3 the reflex discharges in dorsal roots on opposite sides of the lumbar cord, as they are evoked by a shock applied to the sciatic nerve, are brought into contrast.

Reflexes into the dorsal roots can be evoked by stimulation of any one of the adjacent roots of the same or the opposite side. Similarly, reflexes into the saphenous nerve can be elicited by any sensory nerve of the same or opposite limb. The largest reflex, however, is produced when the saphenous nerve itself is stimulated. When shocks of increasing strength are applied, the reflex starts with the first fibers to respond, whether the stimulus is to the saphenous nerve (Fig. 1*d*) or to some other nerve, and it grows as the number of fibers stimulated increases. During the early period of growth the area of the potential of the reflex discharge is in an approximately linear relationship to the area of the potential of the fibers stimulated. The same rule is followed that was shown by Odoriz to hold for discharges into mixed nerves. Some idea of the magnitude of the reflex can be gained from the observation that when weak stimuli are applied to the saphenous nerve, the area of the potential of reflex origin developing in

the nerve may be considerably larger than the area of the potential resulting from the direct excitation (Fig. 1d). As the strength of stimulus is increased, the rate of increase in the size of the reflex falls off, and the addition of high threshold fibers to those of low threshold produces but little augmentation of the reflex response.

*Fibers involved in the reflex.* All the velocities of conduction at which impulses are carried in medullated fibers appear to be represented. C fibers have not yet been detected. That the fastest fibers in the saphenous nerve are utilized is shown simply by taking leads at two distances from the cord. Fig. 4 shows the difference in the time of arrival of the fastest impulses at points 72 mm. apart when the stimulus was applied to the sciatic nerve. The time difference is 0.85 msec., which means a velocity of 85 m. per sec. (at 37.5°C.).

The involvement of slower velocities is shown by the dispersion of the impulses as conduction proceeds away from the cord. Fig. 5 was obtained from the saphenous nerve. A small opening was made over the nerve 70 mm. from the cord for application of the stimulating electrodes, and 120 mm.

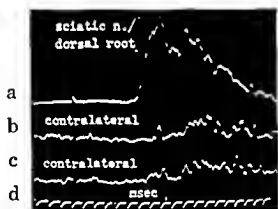


FIG. 3. Comparison between homolateral and contralateral reflex discharges in the dorsal roots of L6. Decerebrated cat. Stimulus on sciatic nerve: *a*, homolateral root. *b*, simultaneous lead from contralateral root in the same level with 5 X amplification. *c*, another record from the contralateral root, showing a somewhat earlier start of the reflex discharge.

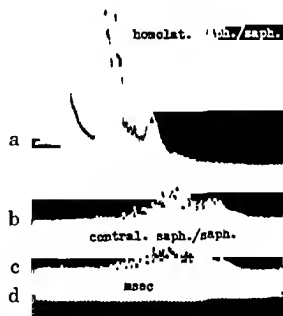


FIG. 2. Comparison between homolateral and contralateral reflex in the saphenous nerve. Decerebrated cat. *a*, stimulus homolateral. *b* and *c*, contralateral stimulus.

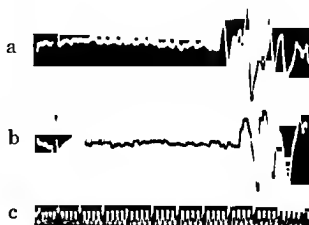


FIG. 4. Conduction speed of the fastest fibers in the reflex discharge of the saphenous nerve, after homolateral sciatic stimulation. Cat under dial. Leads diphasic. *a*, record at proximal lead. *b*, record made simultaneously at a lead 72 mm. distal to *a*, time in msec. and 0.2 msec.

distal to this point the active lead was applied to a bit of the nerve that had been dissected free. The intervening stretch of nerve was left protected by its coverings. After recording the reflex the conduction distance was shortened, so that the lead came in turn to be 80, 35, and 20 mm. from the position of

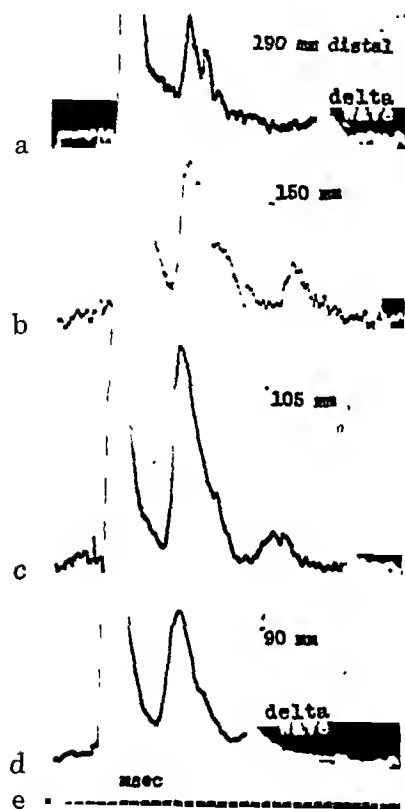


FIG. 5. Conduction speed of the second discharge group (in delta fibers). Stimulus on the saphenous nerve 70 mm. from the spinal cord; leads at the distances from the spinal cord indicated on the records. Cat under dial. The first elevation in all four records is the directly excited afferent volley.

of the reflex is carried in alpha fibers.

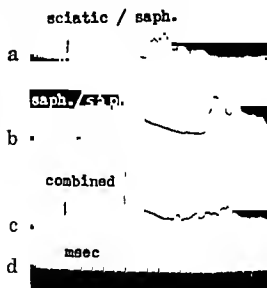
The second discrete wave described above in the saphenous to saphenous reflex, on the other hand, cannot be blocked by an alpha volley. Active delta fibers are necessary. The simplest form of the experiment involves a single stimulus. When the saphenous nerve is stimulated at a strength that will excite only the fibers which contribute the first high elevation in the electro-neurogram, made up of fibers faster than delta (and in this paper called alpha),

A notable feature of the records is the second distinct elevation. As conduction proceeds, the second elevation becomes increasingly separated from the first one, showing that it is made up of slower impulses. Calculation of the velocities shows that the head of the group travels at about 19 m. per sec. In other words, the impulses are in the fibers that give the delta elevation in the saphenous electroneurogram, originally designated as the *B* elevation (Erlanger and Gasser, 1929) or the *B*<sub>1</sub> elevation (Bishop and Heinbecker, 1930). A similar calculation for the velocity of the alpha fibers from the same records gives a value of 78 m. per sec. (35°C.).

Another method of determining the nature of the fibers occupied during the reflex is to oppose the discharge with a blocking volley of known fiber composition. Fig. 6 shows the effect of opposing a volley of alpha fibers in the saphenous nerve to a reflex discharge into the nerve evoked from the sciatic. During the refractory period of the alpha fibers it is apparent that the discharge attributable to the sciatic stimulation is obliterated. The latter part of this discharge, however, escapes the block and becomes merged with the reflex of saphenous origin which now appears in a modified form, because it is inhibited by the central conditioning effect of the sciatic volley. By placing the blocking alpha volley in various positions with respect to the discharge, it can be shown that all of the first large component

a reflex is produced which contains all the components, including the delta group (Fig. 7a). If now the stimulus is increased, so that the exciting volley contains the delta elevation, the delta component of the reflex drops out (Fig. 7b). The afferent delta fibers lag so far behind the alpha fibers that they are

FIG. 6. Blocking effect of alpha fibers. Potentials in the saphenous nerve of a decerebrated cat. *a*, after stimulation of the homolateral sciatic nerve. *b*, after stimulation at alpha strength of the saphenous nerve itself. *c*, both stimuli combined; the saphenous stimulus on the way to the spinal cord meets the reflex impulses coming from the cord.



able to block the reflex discharge into delta fibers which the alpha fibers would produce. In a further refinement of this experiment it can be shown that the delta fibers drop out of the reflex in the proportion in which they are brought into the direct response.

In another form of the experiment, the reflex is produced by an alpha volley as before, and a second volley is employed to produce the blockade. If the blocking volley is made up of only alpha impulses, it is unable to block the second component of the reflex, even when placed directly ahead of the oncoming discharge (Fig. 7c); but if it contains the delta elevation (Fig. 7d) the second component of the reflex is blocked.

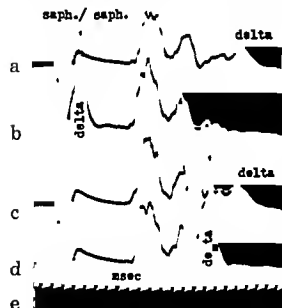


FIG. 7. Blocking effect of delta fibers. All stimuli volley interpolated during the second wave of the reflex. The delta wave in the reflex is unaffected, *d*, as *a*, but with a second afferent volley including delta fibers interpolated during the second wave of the reflex. The delta fiber discharge is again blocked.

The number of fibers in the dorsal roots participating in the reflex is large. A preliminary estimate of the number involved was made in the following

manner. A saphenous to saphenous reflex was recorded so that the area of the action potentials of the afferent volley and of the reflex discharge could be measured. The size of the afferent volley was adjusted so that all the alpha fibers in the nerve were active, in the manner of the experiment recorded in Fig. 1b. The area of the action potential of the volley thus represented all the alpha fibers in the nerve and served as a suitable reference value with which the first component of the reflex discharge (that has just been shown to be carried exclusively in alpha fibers) could be compared.

The area of the reflex is 65 per cent of the area of the spike (inclusive of the after-potential), but this ratio cannot be taken to represent the proportion of the fibers in the reflex because of the possibility of repetition within

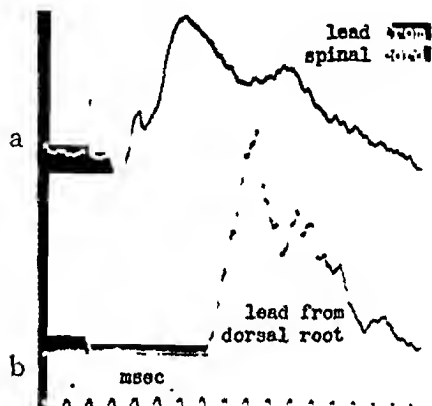


FIG. 8. Reflex time of the dorsal root reflex. Stimulus on sciatic nerve. Cat under dial. *a*, potential on the surface of the spinal cord near entrance of the dorsal roots in L 6 against an average lead outside the spinal cord. The first downward deflection represents the incoming impulses in the sciatic nerve fibers. *b*, simultaneous lead from dorsal root in L 6 about 10 mm. distal from root entrance.

impulses and reflex discharges, or whether some of the fibers are reserved for the latter function only. An answer to this question cannot be given at the present time. All that can be said is that if there are non-sensory fibers in the dorsal roots, they are numerous and distributed over a wide range of velocities.

*Reflex time.* The reflex time is best studied on roots, as little correction is necessary for conduction in the nerve fibers. A special electrode holder was constructed to clamp on to the vertebra adjacent to the root. It carried a pair of hook-shaped silver electrode wires, which could be adjusted to the proper position for picking up the potentials from the root by means of a three-dimensional slide arrangement operating with keystones and spindles. When

individual fibers. The duration of the potential is 8 msec. Therefore, if repetition is taking place, it must occur at frequencies higher than 125 per sec. In the absence of frequencies higher than this figure, 65 per cent would represent the proportion of the fibers involved in the reflex. If higher frequencies occur, they could hardly be expected to be faster than 300 per sec.; that is, one would hardly expect repetition within the compass of the first peak of the reflex potential.<sup>2</sup> The area of the first peak is 35 per cent of the spike area. Thus an estimate that 35 per cent of the alpha fibers are accessible to reflex occupation would be a conservative one, particularly in view of the fact that there is no reason to believe that all the alpha fibers potentially available for reflex activity are involved in this particular reflex.

It would be interesting to know whether all the fibers mediate sensory

<sup>2</sup> The experiments mentioned in the footnote on page 379 confirm this expectation.

in operation, mechanical disturbance of the roots was minimized, even when large reflex movements took place during the observations

A homolateral reflex in the sixth lumbar root produced by a shock applied to the sciatic nerve is shown in Fig 8, along with a simultaneous record of the potential in the spinal cord. The first deflection downward marks the arrival of the afferent impulses at the cord. The large deflection upward is the negative part of the cord potential (Gasser and Graham). The reflex starts 4.2 msec after the arrival of the impulses. When corrected by 0.2 msec for the conduction time in the nerve fibers, a figure of 4.0 msec is obtained for the total synaptic delay in the cord. Thus, of course, is the minimal reflex time. Other impulses continue to be discharged for the next 20 msec. The minimal reflex time is the same, whether it is produced by a weak or a strong afferent volley and is remarkably constant from preparation to preparation, the variation being less than 1 msec.

The synaptic delay in a contralateral reflex is only slightly longer than in the homolateral reflex. Fig 3b shows an additional delay of 1.5 msec in comparison with 3a, and for 3c the additional delay is even less. This interval is long enough, however, on the basis of the unpublished studies of Toennies on the synapse time in the spinal cord, which gave values of 0.55 to 0.8 msec, to allow for the passage of one or two synapses in addition to the number involved in the homolateral reflex. In the latter there is sufficient time for traversing 5 to 6 synapses.

**Reflex summation.** Like motor reflexes, the reflexes over the dorsal roots may be summed and facilitated or inhibited. Fig 9 shows how, as stimulation of one sensory nerve is added to another, the size of the reflex discharge into the saphenous nerve becomes augmented. Stimulation of the tibial and peroneal nerves produces a greater effect than stimulation of either nerve alone, and the combined effect is further increased if a small afferent volley from the saphenous nerve itself is added to the total. The increase in

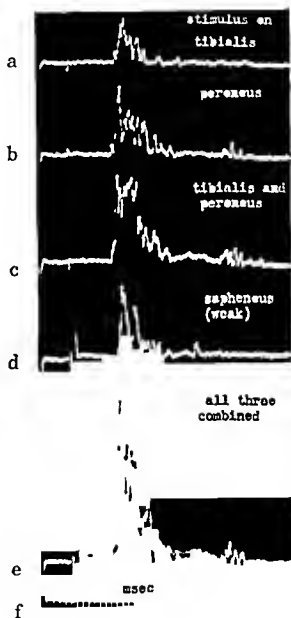


FIG 9 Summation from simultaneous stimulation of the tibialis, peroneal, and saphenous nerves. All leads from the homolateral saphenous nerve. Decerebrated cat. *a*, stimulation of the tibialis nerve at maximal alpha strength; *b*, stimulation of the peroneal nerve at maximal alpha strength; *c*, simultaneous stimulation of *a* and *b*; *d*, weak stimulation of the saphenous nerve; *e*, simultaneous stimulation of *a*, *b*, and *d*.

the reflex might be brought about through occupation of more pathways in parallel or through summation of excitation at the synapses because of activity in adjacent endings occasioned by convergence of impulses from the several sources. Or it might be brought about by a combination of these two possibilities, or by the two overbalancing a certain amount of inhibition. It is impossible to know from inspection of the records how the effect is constituted. However, it is possible to show that facilitation by appropriately timed convergent impulses can take place; and also that the reflex may be inhibited.

In order to demonstrate facilitation it is necessary to show that the effect of two simultaneous volleys is greater than the sum of the effects of the two

volleys in isolation. This condition is met in Fig. 10, in which a dorsal root to dorsal root reflex is facilitated by stimulation of the sciatic nerve. Owing to the longer conduction distance in the sciatic nerve, the first impulses in the volley from this source arrive at the spinal cord 1.2 msec. later than the afferent impulses from the root. As the reflex time is the same in the two instances, the root to root reflex starts earlier than the sciatic to root reflex. When the two sources of the afferent volleys are stimulated simultaneously, it is now seen that in the period during which the root to root reflex antecedes the sciatic nerve to root reflex, the activity in the spinal cord attributable to the impulses from the sciatic nerve is able to increase the reflex discharge of root origin to a size over and above what it would otherwise be.

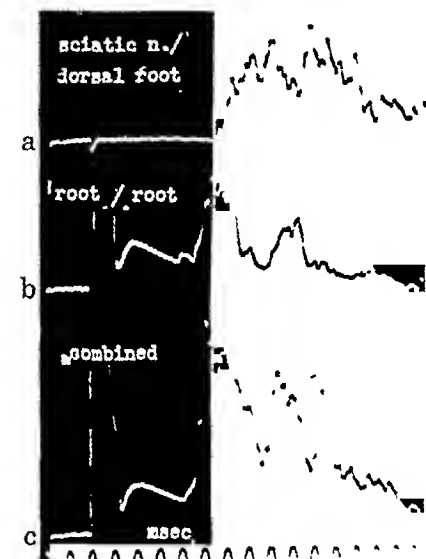


FIG. 10. Facilitation of a reflex discharge into a dorsal root (L 7). Cat under dial. *a*, stimulation of the sciatic nerve. *b*, stimulation of the dorsal root itself. The first impulses arrive at the spinal cord 1.2 msec. earlier than the first impulses from the sciatic nerve. *c*, *a* and *b* combined. The vertical white line marks the time of the first reflex discharge when the sciatic nerve is stimulated. Ahead of this line, the combined reflex is clearly facilitated.

nerve, when the reflex into the saphenous nerve is under observation. The tibial nerve, itself producing only a small reflex, through its central effects is able to bring about a material reduction in the reflex from the saphenous nerve. The conditioning is most obvious in connection with the delta wave. Although the tibial nerve is unable to excite reflexly any of the delta fibers of the saphenous nerve, it is able to inhibit completely the reflex excitation of these fibers from the saphenous nerve itself. Some of the central pathways

*Inhibition.* When two afferent volleys are separated by a short time interval, the reflex produced by the second or testing volley is inhibited by the activity ensuing upon the first or conditioning volley. Fig. 11 shows the inhibitory effect of a stimulating shock to the tibial nerve 4 msec. ahead of a shock to the saphenous

necessary for the reflex must be accessible to tibial excitation and be conditioned thereby in such a way as to make them for the time being unavailable for participation in the reflex.

It was shown by Gasser and Graham that when a single afferent volley arrives at the spinal cord, there is set up in the internuncial neurons a potential which is characterized by an initial negative period, lasting about 20 msec., followed by a positive potential lasting over 100 msec. During the negative period a discharge of impulses occurs into the sciatic nerve (Hughes and Gasser 1934). A cord potential of this sort is shown in Fig. 12, and during the negative period it can be seen that a discharge likewise takes place into a dorsal root.

Hughes and Gasser also showed that as long as the cord potential conditioned by one afferent volley persists, the response to a second volley is inhibited, both in the internuncial neurons and the ventral root reflex, and that the inhibition is greatest at the start and declines over a period of a second. The relationships of the dorsal root reflexes follow in every way those of the ventral root.

When the reflexes are produced in a dorsal root by two alpha volleys from the sciatic nerve, a reflex response to the second volley takes place only when the latter arrives after the completion of the discharge produced by the first volley, *i.e.*, after 10–20 msec. Recovery is slow at first. In Fig. 12 the response in the root 50 msec. after the conditioning volley is only 15 per cent of the unconditioned response. Later the rate of recovery accelerates. At 100 msec. it is 50 per cent, and at 300 msec. 90 per cent. Then the recovery is more gradual and more than a second is needed for its completion. As in the ventral root reflex, the course of the recovery follows temporally that of the internuncial neurons and must be directly dependent upon it. As a whole, the negative cord potential recovers more rapidly than does the reflex, but it must be remembered that the reflex is several neurons removed from the primary neurons, while the potentials in the cord include those in first and second order neurons. The portion of the cord potential that is attributable to higher order neurons does not recover faster than the reflex.

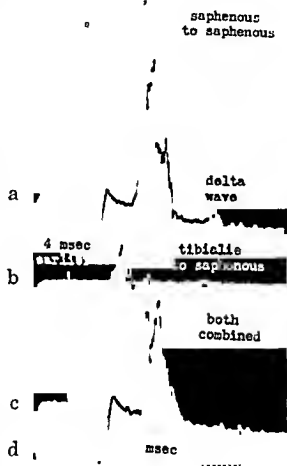


FIG. 11. Inhibition of a saphenous to saphenous reflex by stimulation of the homolateral tibial nerve 4 msec. earlier than the stimulation of the saphenous nerve. *a*, stimulation of the saphenous nerve itself. *b*, stimulation of the tibialis nerve. *c*, *a* and *b* combined. Note the reduction of the alpha group and the elimination of the delta group.



When the reflex in the saphenous nerve is in response to tetanic stimulation of the homolateral sciatic nerve, all the components after the first one are reduced by an amount related to the frequency of the tetanus. Fig. 13 shows the reduction at frequencies of 5 and 12 per sec. As the tetanus

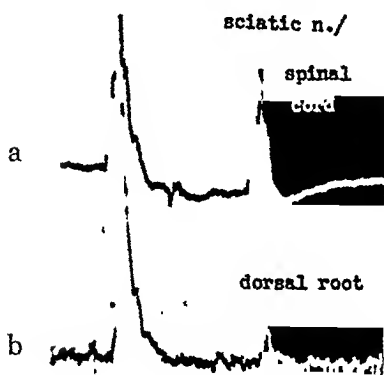


FIG. 12. Simultaneous records of the spinal cord potentials and a dorsal root reflex, showing inhibition of the response to an afferent volley by a response preceding it by 50 msec. Refractoriness of the reflex activity related to the spinal cord potentials. Two shocks of equal strength, maximal for alpha, were applied to the sciatic nerve. Decerebrated cat. *a*, potential at the dorsal surface of the spinal cord at L 6 against surface of cord at L 4. *b*, lead made simultaneously from a strand of the sixth lumbar dorsal root.

because it stood in opposition to the strongly entrenched law of Bell and Magendie.

Rediscovery of the discharges was made by Matthews in 1934, and a more complete description was given in a paper with Barron in 1935. It was recognized that impulses emerge over the dorsal roots in large numbers; but in the interpretation of the phenomenon an explanation was put forward for the majority of the impulses which did not involve their participation in a reflex. The discharges in the larger fibers were divided into two types: secondary or relayed discharges from cells within the spinal cord (type *c*), and antidromic sensory discharges (type *b*). The type *c*

proceeds, the discharges tend to decline progressively, that is, conditioning, or inhibition, is cumulative. At low frequencies the decline is small and the successive components tend to arrive at a steady state. But at higher frequencies the decline is rapid and the discharge takes on the form of a typical "jet" reflex.

### DISCUSSION

Reflex discharges over the dorsal roots were originally described by Gotch and Horsley in 1891. With the slow galvanometers then available they demonstrated reflexly excited activity in dorsal roots after the connection with the ganglion had been severed, and in the sciatic nerve after all the ventral roots had been cut. Their conclusion, which we must now admit to be correct, was that "when a spinal center is thrown into activity, a portion of its energy flows as a discharge backwards down the posterior roots as well as forwards down the efferent fibers of the anterior roots and upwards and outwards along internuncial fibers to the next center." But their observation passed unheeded, probably

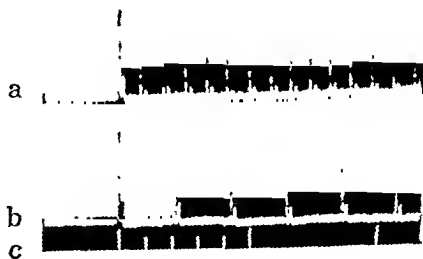


FIG. 13. Response to slow tetanization. Decerebrated cat. Stimulation of the sciatic nerve, lead from the homolateral saphenous nerve. *a*, 12 stimuli per sec. *b*, 4.5 stimuli per sec. *c*, time in 0.1 and 0.5 sec. intervals.

discharges were conceived as having full reflex character. They could be evoked or modified by impulses from widely separated sensory fields on the same or the opposite side of the body, such as the impulses arising from movements of the limbs or head. On the other hand, the major group, or type *b*, was conceived as occurring in fibers that were emerging as a continuation of sensory fibers which had entered the cord through some other root on the same side ("recurrent" fibers). Impulses could be excited in these fibers only from highly restricted areas.

In the course of our observations we have searched for impulses that could be interpreted as being of the recurrent type. The velocities involved are so rapid that impulses entering one root should appear in even quite distant roots within 1 msec. For adjacent roots the time would be a small fraction of a millisecond. But no recurrent impulses have been found. The main discharge, which is a large one, starts regularly after  $4 \pm$  msec. (Figs. 3, 8, and 10a), and even if the amplification is increased up to the noise level, no impulses can be identified as leaving within the first millisecond. Thus the repeated discharges of constant height that are conducted in the centrifugal direction but are not subject to reflex control, which were described by Matthews and which we also have observed in certain preparations, can in our opinion hardly be taking place in recurrent fibers.

The location of the cell bodies from which the fibers involved in the reflex originate cannot be settled by physiological experiment. The evidence must come from histological observation. Hinsey has reviewed the findings and has also performed new experiments of his own. The best supported interpretation appears to be that the fibers arise from cells in the dorsal root ganglia. Since the appearance of Hinsey's review, the subject has been reexamined by Young and Zuckerman. They find a few fibers smaller than  $3\mu$  undegenerated after removal of the ganglion, but they consider that the possibility exists that the fibers may have regenerated from the ventral roots. In any case, as they found no large fibers and as the reflex involves the largest fibers in the roots, it must be considered as occurring in fibers having their origins in the dorsal root ganglia. The conclusion seems to be inescapable that fibers from the dorsal root ganglia make central synaptic connections with internuncial neurons of the cord in such a way that they can be reflexly excited with a resulting discharge of impulses toward the periphery of the body. The question whether or not the fibers which carry these impulses are identical with the fibers carrying the sensory impulses toward the cord has not yet been answered by direct experimental evidence.

#### SUMMARY

1. A description is given of the properties of the reflex discharge which takes place over the spinal dorsal roots of the cat, following stimulation of sensory nerves. Observations were made on the saphenous nerve or on the lumbar roots following stimulation of homolateral or contralateral lumbar roots or sensory nerves of the hind limb.

2. The homolateral reflex produced by a single afferent volley is charac-

terized by an action potential that rises to a peak in 1-2 msec., then declines along a curve which shows two to three secondary crests at intervals of 2.5-3.5 msec. Alpha fibers are involved exclusively in this part of the reflex.

3. When a reflex is produced in the saphenous nerve by a volley of alpha impulses from the saphenous nerve itself, the first reflex wave is followed by a second wave which is separated from it and is carried in delta fibers.

4. The contralateral reflex produced by a single afferent volley is much smaller than the homolateral reflex, but it lasts longer. It starts out gradually and comes to a maximum only after 6-20 msec.

5. The reduced reflex time of the first discharges in the homolateral dorsal root reflex is 4+ msec., and is independent of the strength of the exciting volley. In the contralateral reflex the reflex time is as much as 1.5 msec. longer.

6. The reflex produced by an afferent volley can be conditioned by a second appropriately timed afferent volley in the same or another nerve. Summation, facilitation, and inhibition can be demonstrated.

7. A calculation is given indicating that at least 35 per cent of the alpha fibers in the saphenous nerve are accessible to reflex activation.

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# POTENTIAL RECORDS FROM THE OPTIC CORTEX OF THE CAT\*

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THE FUNCTIONING of the optic pathway of the cat has been studied by the methods previously employed on the rabbit (Bartley and Bishop, 1933, a & b), namely, by recording the electrical responses of its different elements following single and repetitive shocks applied to the optic nerve. The records of this activity show more specific detail than in the rabbit, presumably a correlate of more specific lamellar differentiation in the cortex of the cat. Magnesium sulphate, 0.25 g/K or less, has proved a suitable anaesthetic, with ether administered during operation. Positions of all electrodes were checked in 20- $\mu$  histological sections of the experimental material, and corresponding material is being further studied in Golgi and Golgi-Cox preparations.

Three aspects of cortical relations need to be known for an adequate analysis of the functioning of this cortex as a neural mechanism. Of these, the *anatomical* courses of the connections of the striate area with other parts of the nervous system have been the most extensively studied. The *histological* or synaptic relationships of the neurons to each other in cell masses such as the geniculate body or the cortex are not so well understood, even to the degree to which neurons themselves have been described. The *time* sequences of the responses of such complicated masses of neurons are no less significant, and it is this temporal aspect of function which is most approachable by present physiological technique. We report here, therefore, on certain time relations of the responses of the various neurons of the optic pathway following specific stimulation of the optic nerve, in the hope that this will assist in the interpretation of the relationships of cells in the cortex as revealed by histological methods, as well as in the elucidation of the functional machinery by which a visual impulse traverses the nervous system. Finally, in order that the neurons responsible for the observed activity can be identified in the histological picture, the polarity of the response as recorded in different regions is a significant datum.

## THE CORTICAL RECORD OF RESPONSE TO A SINGLE STIMULUS

The total response recorded from needle electrodes, one deeper than the other in the cortex, can be differentiated into three concurrent series of events (Fig. 1). The first is a succession of short waves of the dimensions of axon spikes, each of one thousandth second duration, and occurring at intervals of approximately one and a half thousandth second. The first of these spikes

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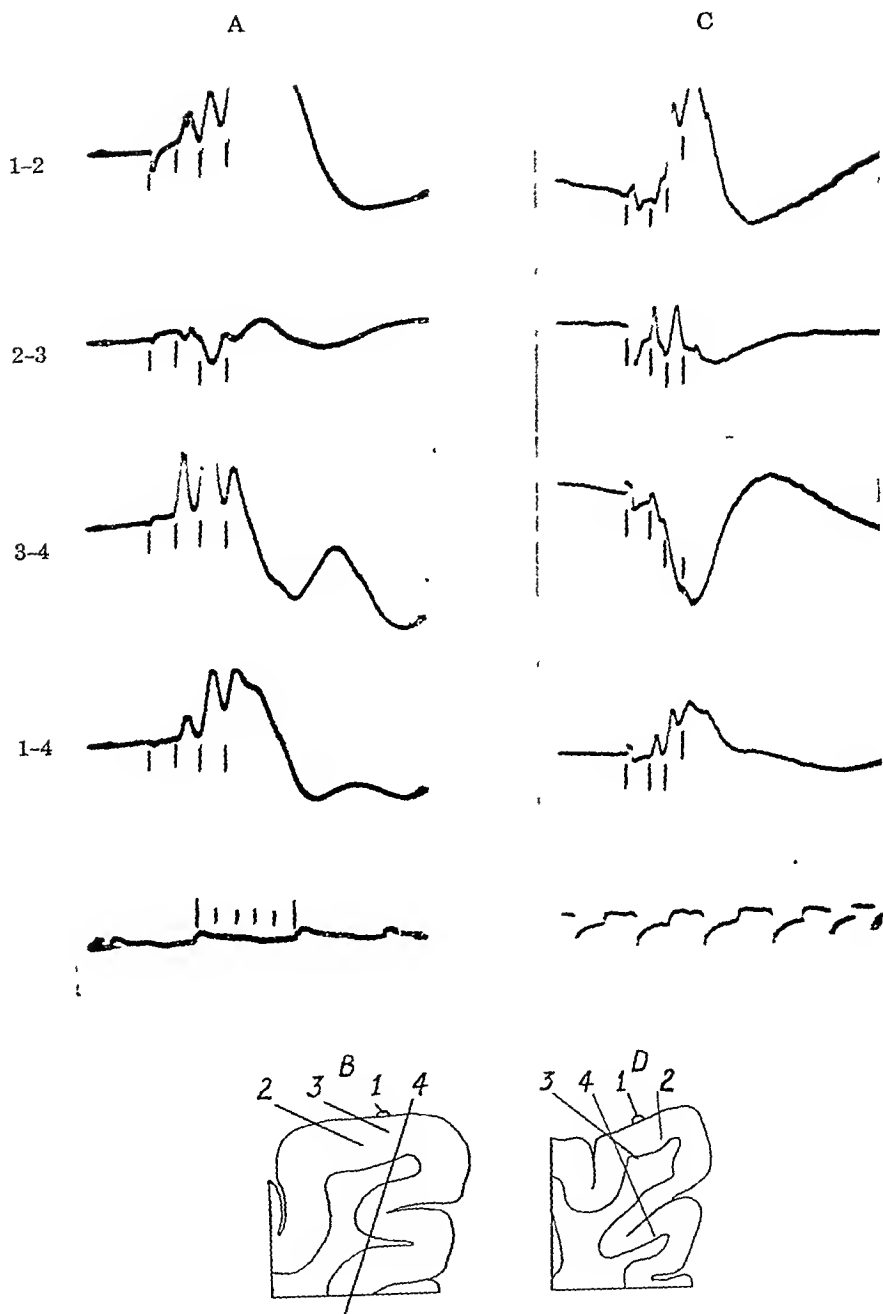


FIG. 1. (See opposite page for explanation.)



wave is absent, or occurs later, but the spike series is present; and under repetitive stimulation, at the proper degree of anaesthesia, these slower waves following the second of two closely timed shocks may fail to appear, leaving the series of spikes inscribed on a flat base line with the same amplitude as they had previously.

The different phases of this series of slower waves represent responses of different elements, not diphasic responses of the same elements. The first two phases can be differentiated by procedures similar to the one mentioned above, that is, under repetitive stimulation the second element may drop out, and the second wave can normally be recorded below the cortex without the first, when both appear at the cortical level. This sequence of waves in the cat is quite similar to a sequence recorded from the rabbit cortex. The third series consists of still slower waves, which also correspond closely to a series in the rabbit. They have the dimensions of the spontaneous alpha waves, may be repetitive after a single stimulus with the frequency of the cat alpha rhythm, and show the same facilitation for a second stimulus as reported for the rabbit. They undoubtedly represent the response to stimulation of the same alpha mechanism which may also respond "spontaneously" in varying degree without specific stimulation of the optic tract. This mechanism, therefore, has at least a double mode of activation, and other evidence indicates that it is played upon by a variety of pathways.

This system of responses is the nearest to a series of volleys that can be conveniently obtained from the cortex; that is, elements of like properties are responding with the maximum synchronization. Stimulation of the retina by light results in temporal dispersion of like elements, due to repetitive and asynchronous responses of optic nerve fibers to even a weak stimulus (Bartley, 1934; Hartline, 1938). Cortical responses so obtained, therefore, do not show details specific enough to afford more than a rough comparison with the sequelae of single shocks to the optic nerve. We suppose, however, that the same sequence of events occurs following the activation of a given optic nerve fiber by either means, with the obvious possibility that fibers in the nerve of different visual significance may activate different types of responses in the cortex.

#### RELATIONS OF OPTIC TRACT TO CORTEX

It is found in both rabbit and cat that the cortical responses are maximal following a stimulus less than maximal for all the fibers of the optic nerve. That is, the smaller fibers of the nerve do not contribute to the activation of the cortex. In preparations with lateral geniculate exposed, the lateral and suprasylvian gyri of the cortex remaining intact, the responses recorded from the gyrus lateralis are as near as we can see quite normal. In such preparations the conduction of impulses through the geniculate and superior colliculus has been recorded. The interpretation of these records is complicated by the fact that the active elements are embedded in the electrolytically conducting mass of the brain, and leads from any part of this mass may pick

up stray currents from the optic tract, as leads from the body surface record the electrocardiogram. Analysis of such records will be reported later, but some of the more concrete results are pertinent here.

Records from the optic tract of the cat, as from that of the rabbit (Bishop, 1933), show two main well-separated waves, followed by a decrementing tail of potential. The first wave propagates at about 60 m.p.s., the second at 25, and there is no potential in the C region. The cortical response rises to a maximum as the strength of stimulus is increased sufficiently to elicit a maximal first wave (Figs. 2 and 3), and within the limits of variation of amplitude of the cortical response as activated at different instants, the second nerve potential is followed by no material change in the cortical record, either of amplitude or of configuration. This calls for a correction of a previous indirect inference to the opposite effect (Bishop, 1933, p. 472). Gudden (1886) states that the large fibers of the optic tract terminate in the lateral geniculate, the smaller fibers passing toward the tectum (quoted from Barris, Ingram and Ranson, 1935). Examination of osmicated sections of the tract at the level of bifurcation into superficial and deep rami just distal to the dorsal nucleus shows qualitatively that most of the superficial bundle consists of small fibers, while the deep bundle contains most of the large ones, and the latter fibers in general turn toward the nucleus. More conclusive evidence is that no post-ganglionic second wave can be recorded from leads, one in the white matter just below the cortex, and one on the cortical surface, while the post-ganglionic first wave is well represented there (Fig. 2). Further, the second wave can be recorded from the tract passing to the colliculus without synapsing, together with a low first wave.

From these observations we conclude that the division of the optic tract fibers into two size groups, as indicated by two discrete potential waves, represents a functional division, as has proved true for other nerves; and that allowing for a slight overlap between the smaller fibers of the large-fiber group and the larger fibers of the small-fiber group, such as usually occurs between adjacent groups, the optic cortex is activated only by the group of fibers of lower threshold and larger size. There are probably five times more fibers in the slower conducting group than in the faster. These findings do not compromise Barris, Ingram and Ranson's (1935) observation that individual fibers divide with branches to both the geniculate and tectal tract, but raise a question concerning the function of the "very small fibers," some of which they observed did so. However, they make no specific statement of the actual size of such fibers. The division into the two waves as recorded should fall at a fiber size of perhaps  $5\mu$  or less in outside diameter, with a possibility of overlap of the first group to a smaller size.

#### TEMPORAL RELATIONS AND POLARITY OF RESPONSES

*Optic tract and radiation.* Conduction in fibers of the optic tract at 60 to 30 m.p.s. requires 0.5 to 1.0 m.s. to the geniculate nucleus. The first wave of the optic tract at this region (Fig. 3) has a duration of not over 1 m.s., of



which approximately 0.5 m.s. is assignable to temporal dispersion through conduction. This leaves about 0.5 m.s. for the duration of the axon responses, which is of the same order as that for peripheral mammalian nerve. This figure is approximate because the necessity of leading from a structure embedded in a conducting medium compromises the precise interpretation of wave form (Bishop, 1937). The interval between the start of this first wave in

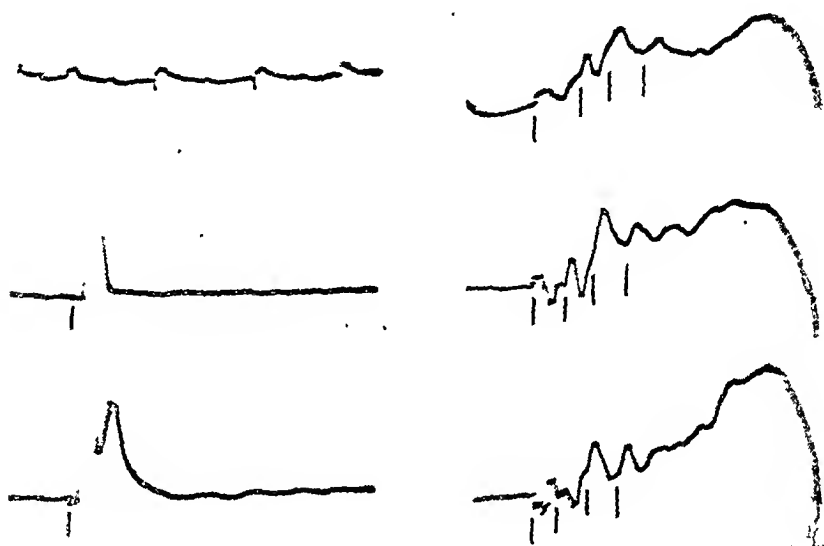


FIG. 2. Relation tract to cortex. Left column, upper, time from 5 m.s. fork; middle, 1st wave maximal led from optic tract; lower, 1st and 2nd waves. Right column, cortical records; electrodes, one on surface of gyrus lateralis, one in white matter of radiation just above ventricle under gyrus suprasylvius. Upper, stimulus strength such that first wave of tract is  $\frac{1}{2}$  maximal; middle, 1st wave maximal; lower, 2nd wave maximal. Stimuli are galvanic currents about 0.5 m.s. duration. The first cortical spike due to the afferent radiation is diphasic, the deep lead becoming negative first. Its later occurrence in the upper record results from the start of the impulse only at the end of the galvanic current with a weak stimulus. In the lower record this first spike is distorted by stimulus artefact. There is no significant increase of the cortical record with the increase of stimulus above the maximum for the first wave of the optic tract. For this and the following figure the lateral geniculate and part of the optic tract were exposed by removal of cortex, leaving the gyri lateralis and suprasylvius intact.

the nerve near the geniculate and the start of the post-ganglionic wave in the radiation is 0.6 to 0.7 m.s., with perhaps 0.1 m.s. assignable to conduction. The synapse time is therefore of the order of 0.5 m.s., which agrees with that (0.5 to 1.4) reported by Lorente de Nó (1935a) for the oculomotor nucleus. The duration of the post-ganglionic spike recorded from the cortex or from the radiation is again less than 1 m.s., that is, there is remarkably little temporal dispersion through the geniculate synapses. The time of arrival of the afferent radiation impulse at the cortex is from 1.5 to 1.8 m.s. in different preparations, under very light anaesthesia, after the start of a maximal

stimulus. No repetitive responses are observed from the tract or radiation after single stimuli to the nerve at just maximal strength.

*Spike series of cortex.* From two leads vertically spaced in the cortex, the afferent spike is recorded at any depth except from the most superficial

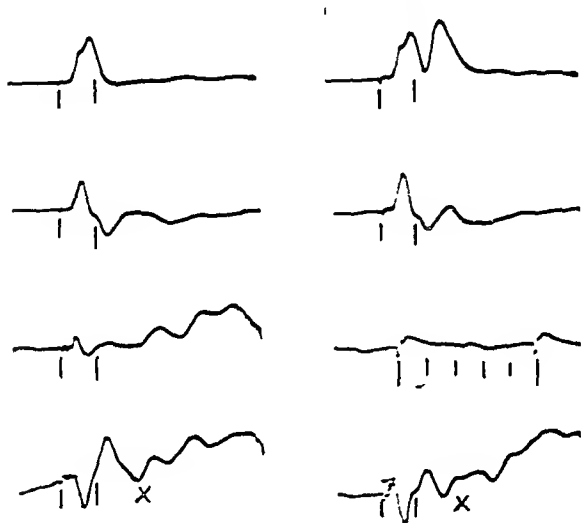


FIG 3 Relation optic tract to cortex Left column, 1st wave in optic tract just maximal, right, 2nd wave maximal Upper, leads from optic tract near geniculate nucleus, and brain stem The double form of the wave is due to an effective double lead, the edge of the wound exposing the tract distal to the geniculate acting as a virtual lead to give the first hump 2nd row, L, one electrode into dorsal nucleus of lateral geniculate, the other along optic tract near edge of wound Up deflection, negativity in tract, downward, negativity in post-ganglionic radiation R, the 2nd wave of the tract appears just behind the radiation wave 3rd row, L, leads from surface of cortex to below radiation A small tract first wave is recorded diphasically, the first cortical spike is the low elevation at the position of the radiation response in the record above, followed by two more spikes and the crest of the slower wave R, time 5 m s 4th row, leads from surface of cortex to geniculate L, first wave of tract recorded downward, radiation response upward as exaggerated first cortical spike R, the second wave of the tract fills the gap between first two cortical spikes at x The top row, 50 mm /mv, 2nd, 100 mm /mv, rest, 200 mm /mv,  $\times \frac{1}{2}$

layers (Figs 1 and 3), and the deeper of two electrodes is always negative to the more superficial. This is presumably because between any two electrodes so placed, exogenous fibers end at cortical synapses, and thus more fibers pass the lower of two electrodes than the upper. This is not true of the second spike,

which may be either diphasic or virtually monophasic in either direction. The interpretation of this finding is reserved until the histology of these preparations has been studied in more detail, but the fact serves to differentiate this spike from the subsequent ones, which are uniformly surface-positive. This difference might be correlated with the fact that cells of certain types have processes oriented in random directions with respect to the cortical strata, while others such as the pyramids are oriented vertically.

The fact that the third and following spikes are surface-positive, that is, that the lower of two electrodes is rendered negative, at any depth in the cortex, presumably means that more elements are active at the lower levels. This might signify that more of the neurons responsible for these spike discharges lie in the lower strata, but more probably means that a greater number of axons of such cells pass the lower of two electrodes, by the number that originate between them. In this sense the polarity of the record does not indicate the direction of conduction, nor does it measure the magnitude of the response at one electrode region, but is rather an index of the histological organization of the cortical neurons. For instance, a *uniform* distribution of active cells throughout the cortex with axons leaving via the white matter should cause by their simultaneous discharge a *progressively increasing* negativity from surface to deep layers. This same distribution of potential should also result from axons entering via the white matter with endings uniformly distributed upwards, but with conduction in the reverse direction from the above.

The passage of the geniculate synapse occupies 0.5 m.s.; the longer interval between spikes at the cortical level (1.5 m.s. from start to start) might indicate a longer synaptic delay, or it might involve passage of two or more synapses. If the latter, we have no evidence whatever of the responses of the neurons involved, the intervals between the spikes being free from recordable potentials. Interpreted literally, this sequence involves the responses of three-neuron chains, consisting of, first, the afferent neuron with cell body in the geniculate, second, an "internuncial" neuron whose axon does not leave the cortex, and third, a pyramidal neuron whose axon leaves via the white matter. In certain records we have observed a spike recorded from the region of the superior colliculus at the time of the third spike of the cortex (Fig. 4), followed, at the colliculus level, but not in the cortex, by a further series of similar spikes. From this we infer activation of the colliculus via the cortex by this spike sequence. In other records a further sequence of spikes at the cortical level may represent repetitive discharges of cortical neurons, but we have not yet traced such discharges beyond the cortex.

This interpretation leaves no place for "self-reexciting chains" of neurons (Lorente de Nó, 1935b) in this particular cortical sequence. There is, however, a suggestion to be made about the function of the multiple connections of the cell networks observable in histological pictures of the cortex. The series of spikes is remarkable in that the spikes do not become progressively longer in duration as the impulses traverse successive neurons, that is, the parallel

discharges in each bank remain in striking synchronization with each other. This should be the result if more than one fiber-impulse were required to fire the next neuron, that is, if summation were necessary. One impulse would then have to wait for reinforcement by a second, and since no repetitive

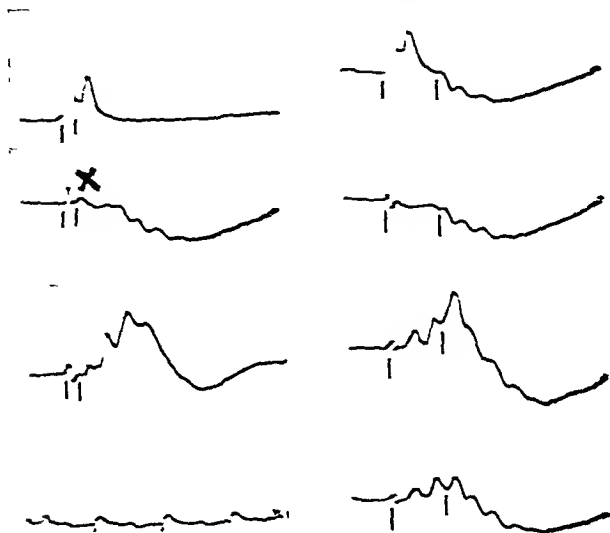


FIG. 4. Relation cortical spikes to colliculus. Upper row, L., two waves recorded from tract and brainstem leads. R., one electrode in tract, one at anterior margin of superior colliculus 1 to 2 mm. below surface. 2nd row, L., electrode in tract, R., surface of colliculus. The wave marked is a recording artifact. 3rd row, L., surface of cortex to white matter below. Three spikes and crest of positive wave. R., surface of cortex to white matter below. Three positive spikes from cortex followed by a series of negative spikes from colliculus as recorded in record above. Note that the largest colliculus spike falls at approximately the same time as the last cortical spike, the following spikes being of opposite sign in the record corresponding to the "diphasic" lead. Also, that the second phase of the cortical slower-wave series is represented in the colliculus response. Lower, L., time in 5 m.s. R., same record as directly above it.  $\times \frac{1}{2}$  amplification. All stimuli maximal for 2nd tract wave.

responses are in evidence, it might have to wait for a response from a parallel neuron which fired somewhat later in the volley. The first neurons active, then, should be unable in general to activate the successive bank of cells until later ones reinforced them, which would thereby prolong the recorded synapse

time and by the same process tend to resynchronize the volley. The multiple connections observed histologically, especially involving certain of the cells with short axis cylinders, might be the means by which such resynchronization was accomplished, as suggested elsewhere from histological considerations (O'Leary and Bishop, 1938).

Perhaps significant in this connection is the effect of increasing depth of anaesthesia, or of rapidly repeated stimulation, upon the cortical responses

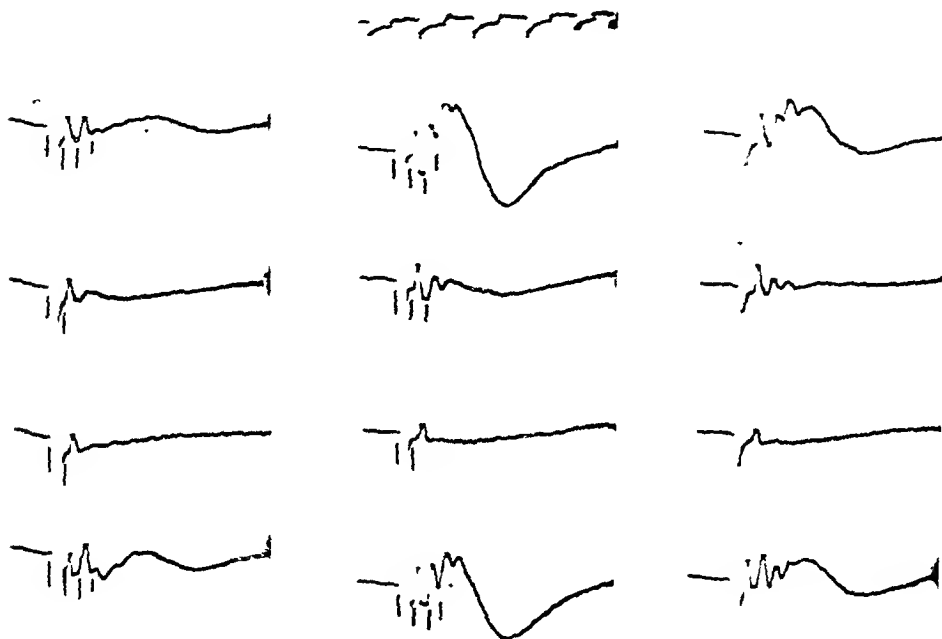


FIG. 5. Effect of ether on cortical record. Left column, leads across middle strata of optic cortex; middle column, across whole cortex, surface to white matter, gyrus lateralis, contralateral to optic nerve stimulated; right column, across whole depth of homolateral cortex. Top row, ether anaesthesia just sufficient to keep animal quiet. 2nd and 3rd rows, increasing ether, respiration still fair, eye wink sluggish. 4th row, recovery. The slow waves disappear before the spikes, the late spikes before the earlier, the afferent radiation (1st spike) only reduced to  $\frac{1}{2}$  amplitude when everything else has been depressed. Time at top, 5 m.s. fork. All records 20 mm./mv. on oscillograph, reduced to  $\frac{1}{3}$  this in reproduction. The homolateral records are over  $\frac{1}{2}$  those of the contralateral cortex in amplitude.

(Fig. 5). The result of ether is to decrease the amplitude of later members of the series before the earlier, without materially altering the duration of the spikes. The last spike to disappear is that due to the afferent radiation, which is much more resistant than are the cortical neurons with longer apparent synapse time. Depressive influences in general should tend to increase synapse time and thence increase temporal dispersion in the volley (since different synapses will vary slightly in excitability). This would be expected to reduce the effectiveness of summation at the synapses, and thus tend to block them.

In such a situation given synapses which were essentially alike in excitability, their apparent "refractoriness" or "synaptic delay" might be a function in part of the temporal dispersion of impulses in functionally parallel pathways.

*Slower cortical waves.* In the foregoing, it appears that if the cell bodies or dendrites of the cortical neurons under consideration give a recordable potential, such potential has the same order of time dimension as does the axon. The problem so far is not to account for the long duration of potentials, but for their brevity. With respect to the second series of potentials, the 5 to 10 m.s. waves, their duration is more nearly what one might expect from post-synaptic axon spikes summed out of phase. The first, surface-positive wave is due to different elements from the second, as shown by various differential procedures; the second is in general half as long again as the first, as might be expected from temporal dispersion across synapses, even if differences in conduction of axons can be ignored in the small distances involved. If, however, the duration of a 5 m.s. wave is to be assigned to dispersion of axon spikes across one bank of parallel synapses, such synapses must have quite different time characteristics from those involved in the spike series. Either they discharge repetitively to a single incoming impulse, or else in apparently co-ordinate pathways the synapse times may vary over a range of 1 to 5 m.s. Further, the second, surface-negative wave does not start until 5 m.s. or so after the start of the first; in other words, if only one synapse intervenes here also, the time for passage of this synapse must be of that order. This is a longer time than that involved in the slowest synapses of outlying ganglia, those between pre- and post-ganglionic C fibers. With only negative and circumstantial evidence to suggest it, one might look in this sequence of events for neuron chain responses, even for self-reexciting circuits.

Such an explanation, rather than the inference of an essentially slow process in structures other than axons, is suggested by the fact that the second of these waves can be recorded below the cortex in regions occupied only by axons, with time and voltage dimensions of the same order as those found in the cortical wave. As a tentative interpretation, the first wave of this series may be assigned to neurons lying wholly within the cortex, like the second of the series of spikes, and seems to be activated, like the second spike process, immediately by the afferent radiation volley; but it may consist of temporally dispersed and successive, if not repetitive, discharges. The second wave may be assigned to elements whose axons leave the cortex, the temporally dispersed discharges of which are recorded either at the cortical level or below it. The difficulty with this interpretation is that this second wave is generally surface-negative, indicating more active elements passing the upper electrode in the cortex than the lower. Since, however, there are many axons from all levels of the cortex which leave by the plexiform layer, or even which discharge over axon branches both upwards and downwards, the polarity of this second wave is not inconsistent with the histological picture.

A third wave apparently belonging to this sequence, surface-positive, is usually low in amplitude and not always detectable. When the response is

depressed, either by anaesthesia or by repetitive stimulation, the later elements fall out definitely before the earlier, and this whole slow-wave sequence decreases before the spike series is materially depressed. The third wave might signalize the further progress of the visual impulse through the cortex. These waves are recorded differently at different depths of the cortex, the first member of the series being often so low that it raises a question whether no activity is going on at a given region, or whether the activity is equivalent at each electrode; the latter being the obvious inference to be drawn from records at other levels. Further considerations of polarity and amplitude may be postponed pending histological study of the material.

*Alpha waves.* The sequence of still slower waves, comprising the setting up by a single stimulus of a series of alpha waves, is essentially similar to that of the rabbit, which has been described elsewhere (Bartley, O'Leary, and Bishop, 1937).

### DISCUSSION

The foregoing attempt at description, rather than analysis, of cortical activity obviously fails to explain its functioning. The key to the desired explanation is the action of an impulse at a synapse, or rather, the action of complex patterns of impulses at synaptic networks. In view of the current plethora of hypotheses as to how the synapse operates, it will not be inappropriate to enquire for a specific situation what this hypothetical action must accomplish. From our records of cortical responses, we infer that there is no single answer; but that certain synapses behave in one way and others in another. The synapses involved in the series of closely synchronized volleys represented by 1 m.s. spikes, for instance, are apparently not operating in the same manner as are those involved in the temporally dispersed waves. Whether such differences are to be referred to differences in temporal or other characteristics of individual synapses, or whether the differences are functions of the patterns of the nerve fiber connections between them, and thus of their interactions, our data do not indicate. From the variety of structure of neurons in the cortex, and the obvious complexity of their synaptic connections, one might infer that individual synapses should differ functionally, as well as that a wide variety of histological patterns should result in a variety of response patterns. At any rate, the problem of synaptic function should be recognized as involving two aspects: first, the question of how any impulse passes any synapse, and second, how an impulse arriving at one synapse on a neuron influences the passage of impulses over other synapses on the same neuron. The multiplicity of synapses on neurons in the cortex indicates the importance of this second aspect for cortical functioning.

The cortical records following a single shock to the optic nerve are perhaps not to be interpreted as records of visual function, although they are obtained from the visual mechanism. Unfortunately, records following the briefest light stimulus to the retina are too diffuse to permit of even such differentiation as single shock records exhibit. At best, the latter indicate merely how the

mechanisms involved can operate under severely simplified experimental conditions. In view of the probability noted above, that the pattern of impulses reaching the synaptic network is a determining factor in the response of such a network, it would be rash to infer correspondences between single shock records and sensory function, and the problem of vision is not the immediate concern of this study. We do not insist that a highly synchronized volley of impulses, from all the axons in the optic nerve, imposes upon the cortex the same pattern of response as does the highly integrated pattern of impulses from the intact retina which is involved in even the simplest turning on and off of a light; to say nothing of the implications of visual pattern and perception of movement. We are rather inclined to fall back upon the shopworn analogy of the nervous system and the telephone exchange, in accordance with which we may study the circuits involved, as circuits. It is, we believe, obvious that much information may be obtained concerning the way these circuits operate, and the nature of the connections involved, by treating the system as a system of *mechanisms*. This may even be an essential preliminary to understanding some of the gossip which the system proves capable of transmitting.

#### SUMMARY

Responses of the optic cortex of the cat to single stimuli applied to the optic nerve consist of three overlapping series of potential waves differing in their time relations, and separable by simple differential procedures.

The most rapid series consists of three or more spikes, of the order of duration of axon spikes, typically surface-positive. A slower series of two or three waves, the first surface-positive, the second negative, shows a duration of 5 to 10 m.s. for each wave. The still slower series has the dimensions and characteristics of the spontaneous alpha rhythm and presumably involves an activation of the alpha mechanism by the stimulus.

Of the spikes, the first is definitely assignable to the afferent radiation, the second to a cortical neuron whose axons have not been recorded below the cortex. In this sense its neurons correspond to intercalary neurons of the cord. The third spike can be recorded below the cortex, and appears to activate a succession of elements in the superior colliculus.

Comparison of the time relations of responses from the various levels of the optic pathway yields the following information. Of two well-defined waves in the optic tract showing different conduction rates and thresholds, only the faster is associated with a cortical response, the slower propagating past the geniculate to the superior colliculus without a synapse. The synapse time of the impulse at the geniculate level is of the order of 0.5 m.s. The time lost at the synapse between afferent radiation and the second spike neuron in the cortex is 1.2 to 1.5 m.s., and between this latter and the third spike neuron is the same. The slower first wave starts during the second spike.

The configuration of these various components of potential varies with the depth from which they are led in the cortex, suggesting the possibility that they can be correlated with the details of cortical structure.



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# A SENSORY CORTICAL REPRESENTATION OF THE VAGUS NERVE

WITH A NOTE ON THE EFFECTS OF LOW BLOOD PRESSURE  
ON THE CORTICAL ELECTROGRAM

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## I. INTRODUCTION

The use of cerebral potentials evoked by various peripheral stimuli has proved of value for the study of cortical localization. Of especial interest are the findings of Bartley and Bishop, Kornmüller, Fischer, Wang, Bremer on the visual area; of Kornmüller and of Bremer on the acoustic area; of Spiegel on the vestibular area; of Bartley, of Bard and his collaborators on the central region; of Ectors on the gustatory and masticatory area; of Walker on the cerebellocortical projection; of Gerard, Marshall and Saul<sup>7</sup> on cutaneous, auditory and optic areas. Kornmüller<sup>10</sup> demonstrated the perfect correspondence of the limits of the visual area, determined oscillographically, with those of the area striata determined histologically.

It seemed desirable to investigate a possible sensory representation of the vagus nerve in the cat's cerebral cortex, for this nerve is composed predominantly of sensory fibers (Foley and Dubois,<sup>6</sup>) including, in the cat, the depressor bundle. It is true that most of these fibers constitute afferent pathways of visceral and respiratory reflexes which do not reach consciousness but this does not exclude the possibility of a cortical representation. On the motor side, a cortical control of visceral functions is now well established (Spiegel,<sup>16</sup> Fulton and Kennard,<sup>8</sup> W. Smith,<sup>14</sup>) and indeed the existence of a reflex visceromotor arc passing via the cortex is indicated by the lasting vasomotor disturbances which follow the ablation of certain cortical areas (see Kennard<sup>8</sup>).

Further, the demonstration of a cortical representation for a visceral afferent nerve would furnish a physiological basis for the common view that disturbed coenesthesia contributes to the pathogenesis of various mental affections. Finally, the inhibitory effects, on all the reflex spinal mechanisms, which result from electrical excitation of the depressor nerves (Schweitzer and Wright,<sup>13</sup>) should be reflected in potential changes in the isolated encephalon on stimulating the vago-depressor nerve. These studies led us to examine also the effects of lowered blood pressure on the spontaneous electrical activity of the cerebral cortex.

## II. METHOD OF INVESTIGATION

The central end of a cut vagus was stimulated electrically while the spontaneous electrogram of some cortical region was being recorded and any modification noted. All accessible cortical regions were explored. The normal excitation of vagal receptors would have been preferable, but would have been technically difficult and less likely to yield de-

tectable cortical effects. Since depressor nerve fibers are included in the vagus nerve, excitation of this latter is complicated by a fall of arterial blood pressure which it was important to eliminate. This was achieved, and the disadvantages of narcosis obviated as well, by use of the "isolated encephalon" preparation which was introduced by one of us and has already permitted the registration of cortical reactions to varied corticopetal influences with particular clearness.<sup>3</sup> In these experiments, high spinal section practically eliminated all reflex vasodilation, and bilateral section of the vagi similarly eliminated reflex cardio-inhibition.

The cerebral hemisphere was exposed under ether anesthesia, then the vagi isolated in the neck and the trachea cannulated, and finally the suboccipital region exposed and the spinal cord severed from the bulb with a spatula. Artificial respiration was then initiated and the blood pressure registered from the femoral artery. Animals prepared in this way remained in good condition for hours with a blood pressure between 80 and 100 mm. Hg. When it began to fail it could be maintained by a small dose of ephedrine. The vagus nerve was stimulated by induction shocks at 24 to 50 (make and break) per sec. of sufficient strength to evoke a maximal cardiomotor reflex when the other vagus was not cut. The cortical potentials were led off by a pair of electrodes (Ag—AgCl—Ringer), about 4 mm. apart, placed directly on the cortex, and recorded by a Mathews or a Dubois oscillograph. The experiments were carried out in a completely shielded room with the inductorium separately shielded. In most experiments the sensitivity was 15 mm. for 100 microvolts. The oscillograph frequencies were 5,200 (Mathews) and 2,000 (Dubois).

### III. EXPERIMENTAL RESULTS

With both vagi severed, stimulation of the central end of either one produced no definite alteration of the electrical potentials of the suprasylvian, ectosylvian, cruciate, proreate, occipital or temporal regions or the medial surfaces of the cerebral hemispheres. This negative result cannot be at-

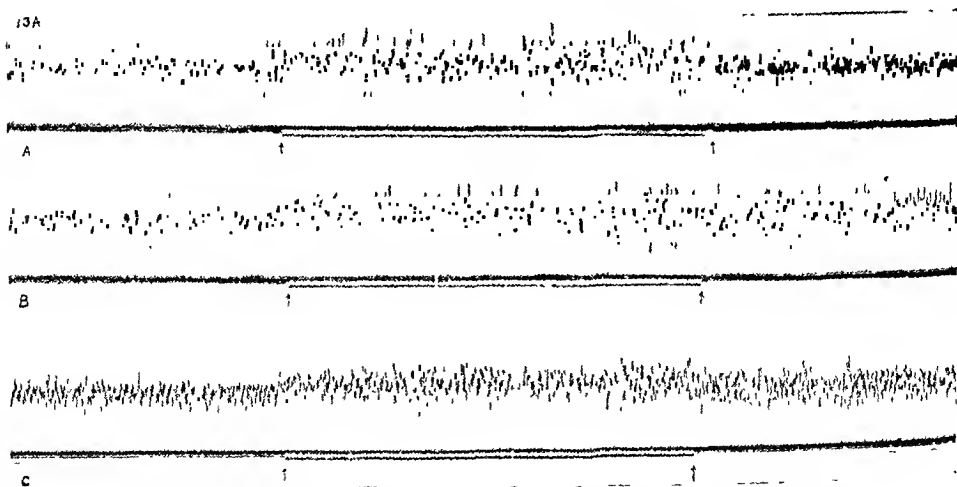


FIG. 1. Cat No. 13. Duration of stimulation indicated by arrows.  
Time in seconds. Other explanations in text.

tributed to a synaptic block in the bulbar center of the nerve, for it contrasted with the clearcut bulbopontine reflexes of the same stimulation: cardio-inhibition and decreased blood pressure (when the second vagus was not cut), and movements of licking and mastication. Further, after removal of

the eyeball and roof of the orbit, a positive effect was repeatedly obtained on the orbital surface of the frontal lobe (anterior composite gyrus), its potentials being increased both in amplitude and rate. The effect seemed to be slightly more pronounced contralaterally. It was never very marked, but undoubtedly, since it was obtained with the same technique which repeatedly gave negative results on other areas of the cerebral cortex, even the adjacent cruciate gyrus of the same animal, and since it disappeared when the nerve was ligated proximal to the electrodes. A typical experiment is shown in Fig. 1.

*Cat. No. 13. December 1, 1937. Left eyeball removed, and the roof of the left orbit, exposing the orbital surface of the left frontal lobe. Both vagi prepared and sectioned. Spinal cord sectioned at C<sub>1</sub>. Artificial respiration. Stimulation with 50 shocks per sec.*

A. Blood pressure 90, pulse 120. Stimulation of central end of the left vagus. Leads on orbital surface of left frontal lobe. Definite increase in electrical activity.

B. Blood pressure 82, pulse 120. Stimulation of central end of the left vagus. Leads on orbital surface of left frontal lobe. Definite increase in electrical activity. Stimulation central end of left vagus. Definite effect as in A with perhaps slight after-effect. Blood pressure by puncture of carotid artery 82, pulse 120.

C. Stimulation central end of left vagus. Definite effect as in A with perhaps slight after-effect. Blood pressure by puncture of carotid artery 82, pulse 120.

The immediate effect is much the same on stimulating either vagus, but the after-effect is more pronounced contralaterally.

Another experiment in which other areas of the cortex were explored in the same animal is shown in Fig. 2. The differences in the electrograms of the different cortical areas is evident in these records.

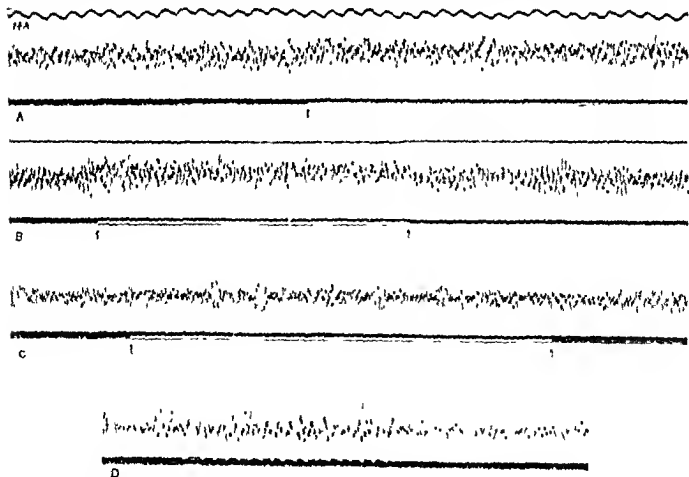


FIG. 2. Cat No. 14. Duration of stimulation indicated by arrows. A and C, cruciate gyrus; B, orbital gyrus; D, ectosylvian gyrus. Time in seconds.

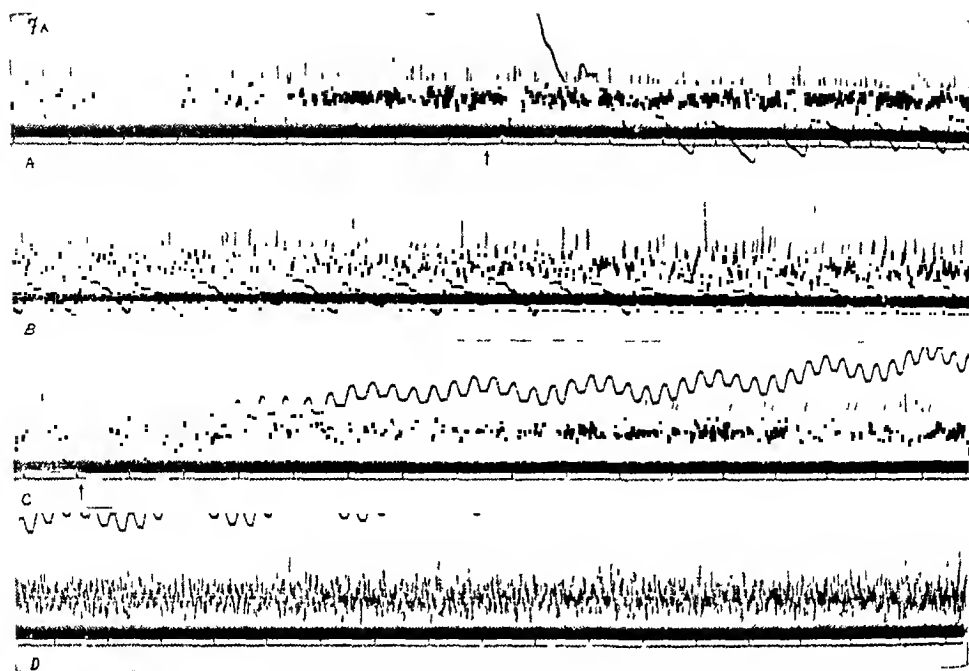


FIG. 3. Cat No. 7. Stimulation indicated by arrows. Time in seconds. Suprasylvian gyrus.

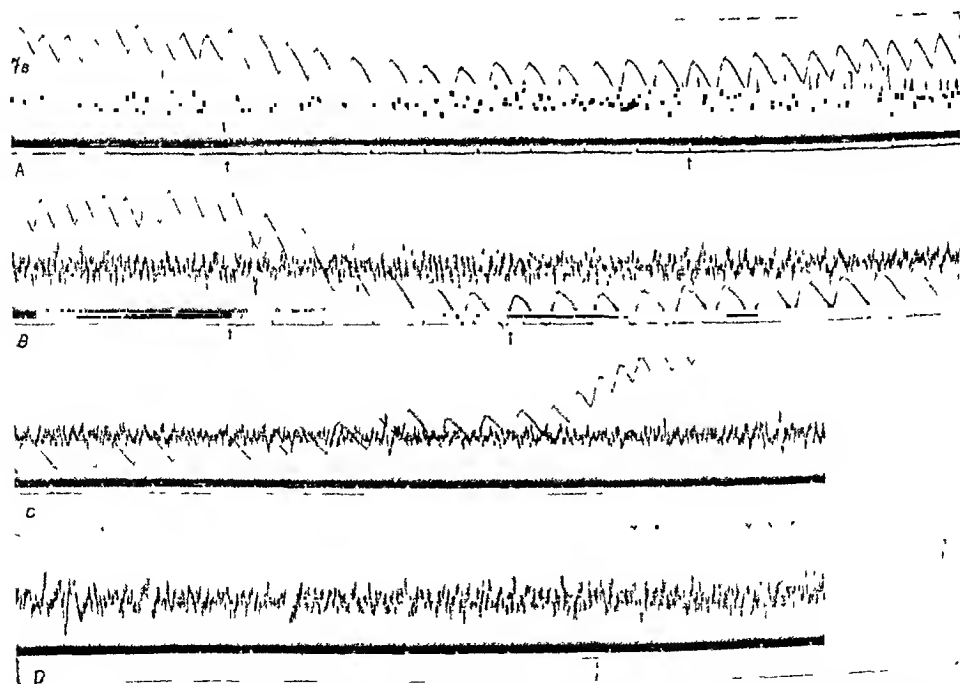


FIG. 4. Cat No. 7. Stimulation indicated by arrows. Time in seconds. Suprasylvian gyrus.

*Cat No. 14. December 3, 1937.* The left eyeball was removed and the entire frontal pole of the left cerebral hemisphere uncovered. The spinal cord was sectioned at  $C_1$ . (Artificial respiration.) Both vagus nerves prepared and sectioned. Stimulation at 50 per sec.

A. Blood pressure 80, pulse 120. Stimulation at central end of the left vagus. Leads on left gyrus cruciatus. No effect on electrical activity.

B. Blood pressure not registering but heartbeat strong at 120 per min. Leads on the orbital surface of the left frontal lobe. Stimulation of the central end of the left vagus. Definite increase in electrical activity which outlasts the stimulus about 5 seconds.

C. Blood pressure not recording but heartbeat strong at 132 per min. Leads on the left cruciate gyrus. Stimulation of the central end of the left vagus. No effect on electrical activity.

D. Leads on left ectosylvian gyrus after exposure of the posterior part of the left hemisphere. Heart weak at 148 per min. The cortex still reacts clearly to stimulation of the left auditory nerve by means of a clacking noise.

Considerable time and some blood were lost between tracings C and D but the cortex was evidently still in condition to react to sensory stimulation.

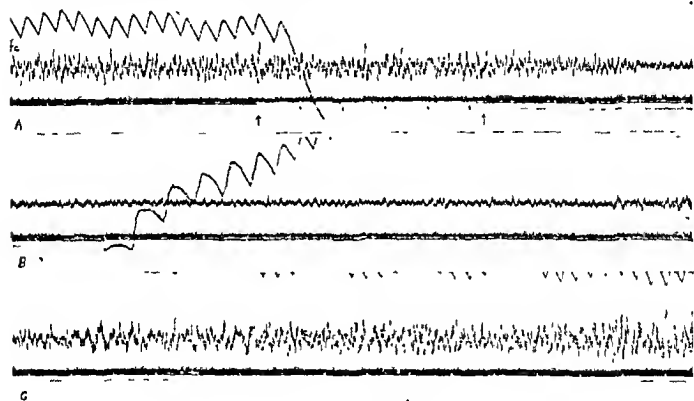


FIG. 5. Cat No. 7. Continuation of Fig. 4.

In all experiments with both vagi severed no effect was ever produced on the state of somnolence of the animal, but in one with the right vagus intact stimulation of the central end of the left repeatedly awakened the cat from a light sleep. This awakening followed a temporary marked decrease in the electrical cortical activity, which was proven to be due to a fall of blood pressure as a depressor reflex through the right vagus. This led us to investigate the effect on the cortical electrogram of variations in blood pressure produced by stimulating the peripheral end of the vagus. A typical experiment is shown in Figs. 3, 4, and 5.

*Cat No. 7. November 3, 1937.* Both vagi exposed and sectioned. The left cerebral hemisphere exposed and leads on the suprasylvian gyrus. Spinal cord sectioned at  $C_1$ . Artificial respiration. Stimulation by inductorium. Time marked in seconds.

FIG. 3. *A.B.C.D.* (Read all records like a book from upper left to lower right.) Blood pressure 100. Pulse rate, 160. Peripheral end of left vagus stimulated with secondary coil at 27 cm. Blood pressure dropped to 60–70; pulse slowed to 66. Form of electrical activity altered. Effect outlasts the stimulus but disappears with rise in blood pressure.

FIG. 4. *A.* Blood pressure 90. Pulse rate 138. Peripheral end of left vagus stimulated. Secondary at 26 cm. Blood pressure dropped to 60; pulse rate to 92. Very little effect on the electrical activity. Pressure afterwards rose to 95 and pulse to 142. The electrical activity became more regular. *B.C.D.* Stimulus was repeated with the coil at 25 cm. Blood pressure dropped from 95 to 40, pulse rate to 72. The electrical activity practically disappeared. The effect outlasted the stimulus about 20 seconds and persisted over 7 seconds after the blood pressure returned to its former level. Blood pressure rose to 100, pulse to 142. Electrical activity much improved and resembles that in Fig. 3.

FIG. 5. *A.B.C.* Blood pressure 80, pulse rate 144. Peripheral end of left vagus stimulated. Coil at 23 cm. Blood pressure dropped to zero and heart stopped. Electrical activity disappeared after about 9 seconds. Electrical activity reappeared 10 seconds after the blood pressure reached its former level. Blood pressure rose to 90, pulse to 186, and electrical activity improved over initial activity before stimulation.

These effects were repeated many times and the records show that a fall of blood pressure below a certain critical level, different for each animal, invariably causes a decrease in the electrical activity of the cortex. With an initial blood pressure of 100, a brief fall of 20 mm. may cause no effect and a longer fall only an alteration in the form of potentials (Fig. 3), whereas in the same animal with an initial pressure of 80, a fall of 20 mm. may result in very marked diminution of electrical activity. The electrical changes follow promptly on the fall of blood pressure but never before several seconds (Fig. 5, *B*). When pressure is restored, the cortical electrogram returns almost instantaneously (Fig. 3 *C*) unless the hypotension has lasted more than ten seconds (Fig. 5), and is complete unless the duration of the hypotension was over 20–30 seconds. The return to its previous state is in general preceded by a short phase of augmentation in amplitude and frequency of the waves (Fig. 5 *C*) related to a phase of high pressure probably due to adrenalin liberation. This phase of increased cortical activity may be accompanied, when the animal was asleep before the vagal excitation, by oculofacial manifestations of awakening. The prolongation of complete cerebral ischaemia for much more than 30 seconds causes irreversible alterations in the cortex even to the complete disappearance of its spontaneous activity and response to sensory stimuli. Moderate hypotension maintained during a sufficient time has a particularly interesting action on the cortical electrogram because at first sight it does not appear to be a depression: the waves, which are reduced in frequency and tend to occur in groups, are greatly augmented in amplitude (Fig. 3 *B*, and *C*). This oscillogram is characteristic of sleep and there are other symptoms of this state (closure of the palpebral fissure, downward rolling of the eyeballs, myosis, spreading of the nictitating membrane). Slowing of the heart produces no effect on cortical potentials if the blood pressure is not altered.

#### IV. DISCUSSION

Little is known of the function or relationships of the orbital cortex of the frontal lobe.<sup>15</sup> Electrical stimulation of this region in man has produced noth-

ing The area in the cat responding electrically to central vagal stimulation would correspond in man roughly to the area FG of Economo.<sup>5</sup> The areas FF, FG, FH are the most granular in the frontal cortex but their efferent and afferent connections are unknown. We were much surprised to obtain an effect from vagus stimulation in this region, it was tested as a matter of routine exploration. It is on the orbital surface of the frontal lobe, in what we take to be the inferior posterior extremity of the gyrus compositus anterior and, so far as we can judge, is the region from which Smith<sup>14</sup> obtained maximum inhibitory effects on respiration.

The effect of lowered blood pressure on the cortical electrogram is doubtless due to anoxemia, since the alterations it sets up closely resemble those which may be produced by cessation of artificial respiration. Further, the cortical manifestations of sleep are seen in the initial phase of anoxemia (Bremer and Thomas<sup>4</sup>) and during moderate hypotension.

Low blood pressure always depresses cortical electrical activity, though differences in the degree or duration of the fall lead to diverse details, from reduction of frequency and tendency to grouping through simple enfeeblement to complete disappearance. Here again the action resembles that of anoxemia (Bremer and Thomas<sup>4</sup>). We have never observed irritative or epileptiform phenomena, in harmony with the prevalent belief in a subcortical origin of the convulsions observed in sudden hypotensive states in man, notably in the Stokes-Adams syndrome. On the other hand, excitation of the central end of the vago depressor nerve did not diminish cortical activity except when, due to preservation of the cardiomodulator reflex, it lowered blood pressure. Our experiments, therefore, do not support the hypothesis of a direct inhibitory action by depressor nerves on the cortex or diencephalon.

## V SUMMARY

1 Stimulation of the central end of the vagus nerve increases the electrical potentials of the orbital surface of the frontal lobe of the cerebral cortex. No other portion is affected.

2 The cortical electrogram is very sensitive to alterations in blood pressure, which may vary both its amplitude and form.

3 The effects of low blood pressure are doubtless due to anoxemia since they are practically identical with those produced by cessation of artificial respiration.

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# DISTRIBUTION OF DISTURBANCE-PATTERNS IN THE HUMAN ELECTROENCEPHALOGRAM, WITH SPECIAL REFERENCE TO SLEEP

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## INTRODUCTION

EARLY study of the cerebral cortex in animals led to the view that this region of the brain acted as a whole. Later work, however, indicated the existence of motor and sensory areas with an extraordinary amount of detailed representation, and also large association areas not directly projected to muscles or sense organs. In man the latter regions make up the greater part of the cerebral cortex. Do the various areas which are known to be functionally different exhibit corresponding differences in brain potential patterns? Particularly, does any change or disturbance in pattern which results from stimulation remain localized or affect the cortex generally?

Recent work in this field has led to somewhat divergent views. Berger (1933, 1934, 1935, 1936) has stressed the activity of the cortex as a whole and Foerster and Altenburger (1935) have also obtained similar records from very different architectonic areas of the human brain during operations. On the other hand Adrian and Mathews (1934) and Adrian and Yamagiwa (1935) originally localized the origin of the alpha rhythm in the occipital lobe, a focus in each hemisphere moving a few cm. right and left or up and down. They attribute the occurrence of a low amplitude alpha rhythm in top and front areas to electrical spread of potentials. Jasper and Andrews (1936, 1938) observed marked differences in pattern of the motor (chiefly beta) as compared with the occipital (chiefly alpha) region. They found little difference between homologous areas of right and left hemisphere in normals; very dissimilar and completely asynchronous patterns in pathological cases. In animals, Kornmüller (1935) has stressed the differences in pattern from cytologically different areas in the rabbit, whereas Rheinberger and Jasper (1937), by permanent electrodes in the cortex of the unanesthetized cat, have been unable to find consistent differences in different areas because of variation in the activity of one region at different times. Stimuli gave rise to specially marked changes in one region but there was also some effect on all other regions.

Our own experiments on man have led us to an intermediate view. There is undoubtedly a localization of certain potential patterns in definite, decidedly large areas of the cortex but there is certainly not the precise localization of pattern that might be expected from the anatomical or physiological map. The brain behaves more or less as a whole so far as electrical activity is concerned. In no respect is this better seen than as the result of disturbances, either internal or due to stimuli sent to the person, awake and asleep. It is

the purpose of this paper to describe the regions of the cortex affected by such stimuli and to present a general picture of potential distribution.

It must be clearly understood that we are not dealing with "evoked" potentials, *i.e.*, potentials appearing in the particular sensory area after peripheral stimulation. In animals these potentials, described by numerous investigators, have a definite form and a relatively short duration. In man their detection through the skull and scalp is unusual. They have been described for light stimuli by Jasper and Cruikshank (1937) in the occipital region, and for touch stimuli by Jasper and Andrews (1937) in the precentral region. Perhaps the flicker potentials of Adrian and Mathews (1934) are to be regarded as evoked potentials.

We are concerned with the more or less continuous spontaneous rhythms whose pattern or appearance may be affected by external stimuli. Three points are of particular interest. Are the waves in different regions of the same general pattern or frequency; are they synchronous and in phase; are interruptions of a train of waves synchronous over large cortical areas? Development of an entirely new recording device with six completely independent amplifier systems has made it possible to study six different regions of the brain simultaneously.

#### ELECTRODE POSITIONS

Much of the disagreement in interpretation of potential records comes from placements of electrodes. There has been extended discussion of the relative merits of the "unipolar" and the "bipolar" methods, both of which have their own particular advantages. Where two small electrodes are used, the potential difference between regions under each of them is measured. Potential changes in the region between them only show if electrodes are close together and the potential is large. Where one electrode is large ("indifferent") and one small the average of the potential changes under the large electrode compared with the small electrode is measured. A simple method is to have one electrode on a region which remains equipotential so that the pattern will represent only what is happening under the other electrode (the unipolar method). If, however, small electrodes are fairly close together (the bipolar method) they will detect differences of potential within a small area of the brain under them, and consequently give the pattern of potential in that region. However, much higher amplification is necessary. This method has two disadvantages: (1) if the whole area is changing in potential simultaneously, no difference of potential is recorded. (2) If one electrode happens to be in an area of one pattern or frequency and the other in an area of another pattern or frequency both patterns or frequencies will appear.

Therefore, we have adopted the policy of comparing some region on the head with a neutral region, the ear or the mastoid process behind the right or the left ear. Bone is thick over the mastoid process and greatly attenuates potentials, for little brain rhythm is observed when the mastoid is compared with the chin or arm or when right and left mastoids are compared with each other, although the electrocardiogram may appear. Care should be taken

not to use a region just above the mastoids behind the ear for brain potentials may be obtained from this region.

Fundamental to the whole interpretation is a knowledge of the amount of electrical spread (extension of the electrical field) as distinct from the physiological spread of potentials. Detection of electrical spread is dependent on the amplification. Adrian and Mathews (1934) assumed that the electrical spread was considerable and explained the fact that the alpha rhythm between vertex and frontal electrodes is one-third the amplitude of that between vertex and occiput, by electrical spread from the occiput. We believe the explanation is this:—that the alpha rhythm is also present in the frontal region and one-third the amplitude of that in the occiput. There can be very little electrical spread with the amplification we have been using. If so, a potential change of  $100\mu$  V in the occipital region should *always* appear at some constant fraction of this value in the frontal region, and *vice versa*. Actually we observe many large potentials from one electrode which do not appear on others.

Gibbs, Lennox and Gibbs (1936) likewise find large petit mal potentials, both spikes ( $1000\mu$  V) and slow waves appearing from the frontal electrode without a corresponding indication in the motor region, both compared with ear. After one second, however, slow waves synchronous with those of the frontal may also appear in the motor region, but without spikes. In this case there must be physiological (not electrical) spread of a disturbance from frontal to motor regions giving rise to the slow potentials. The evidence is perfectly clear that in epilepsy the spread of potentials over the cortex corresponds with the spread of external clinical signs. When the disturbance reaches the motor region it advances and causes movements which reflect the well known Jacksonian progression.

Only with movements of the eyeball is there evidence of electrical spread of potential. Since the retina is negative to the cornea, quick movements of the eye appear in a record. Simultaneous records from different regions indicate that an excursion corresponding to  $150\mu$  V from an electrode just above the eye is reduced about half on the top motor region and one quarter on the occiput. The relative amplitudes differ in different persons. Potentials from eyeball movements, however, are of a totally different character from those of the cortex. They represent rotation of a large dipole, whereas brain potentials represent alternate positivity and negativity of a thin layer in the cortex with respect to the ears or to some other region.

By comparing six different regions of the scalp (front, top and back on both right and left sides of the head) with the mastoid bone, as shown in Fig. 5, we can obtain a very good idea of potential distribution over the whole head. Results may be checked by comparing any of the six electrodes with each other, giving their potential differences directly. Thus, if right and left occipital regions are changing in potential synchronously, in phase and with the same amplitude, no potential will appear between them. If either frequency or amplitude or phase is different, just as marked rhythms may be recorded between right and left occiput as between the occiput and mastoid.

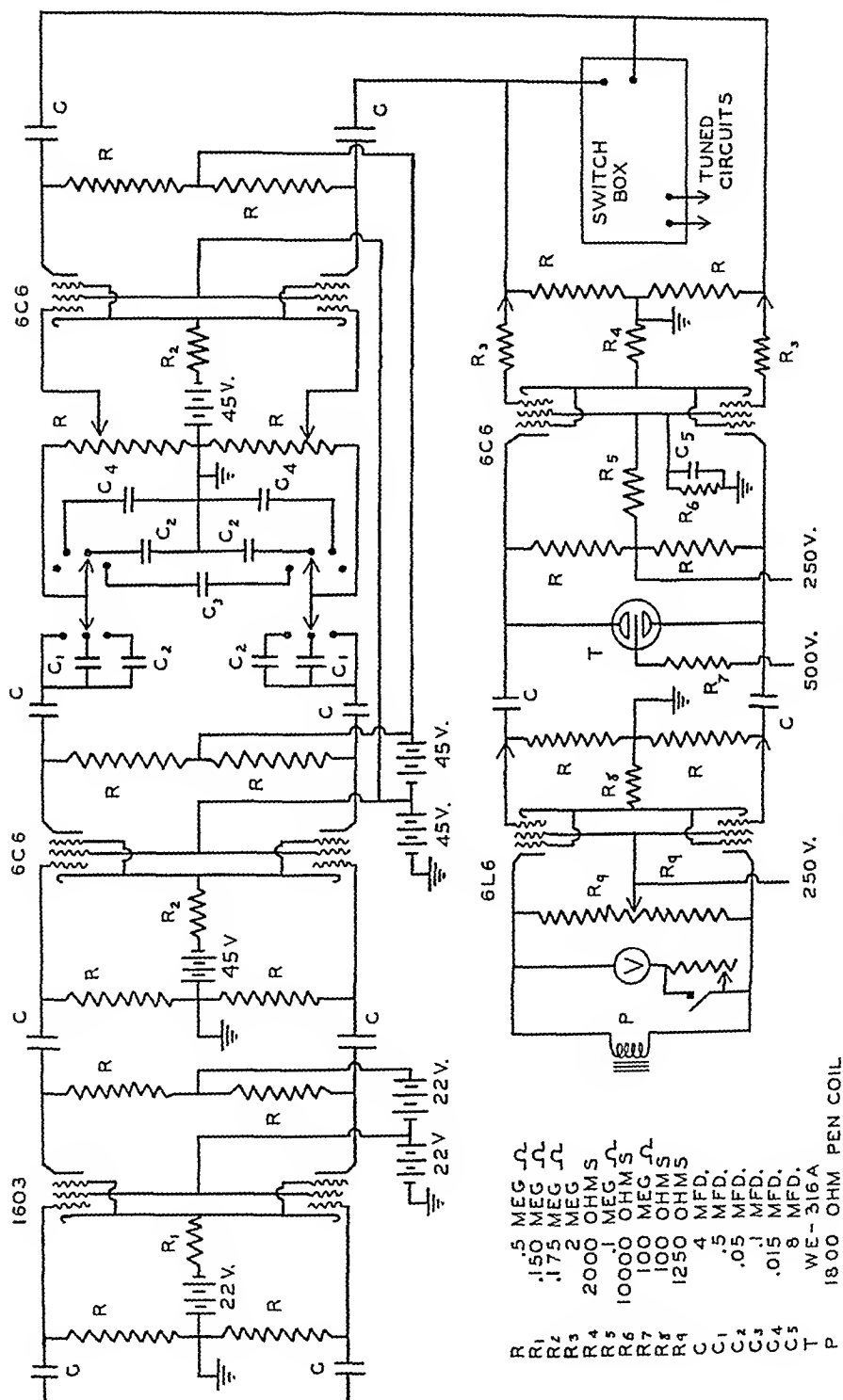


FIG. 1. Amplifying system.

## APPARATUS

A convenient and rapid method of placing electrodes is as follows:—attach a ring of rubber (1.5 mm. thick, 5 mm. inside diameter, 10 mm. outside diameter), cut from rubber tubing, to the scalp with rubber cement which dries rapidly and holds firmly. Abrade the skin inside the ring slightly and apply a little Sanborn electrode paste. Push a 5 mm. disk of silver to which a fine wire is attached into the rubber ring against the skin. A drop of collodion over the disk will prevent evaporation. Shielded wires lead from the electrodes to a switching box where twelve connections can be made to six complete amplifier systems in any possible combination, i.e., any grid can be connected to any electrode or any number of grids to any electrode.

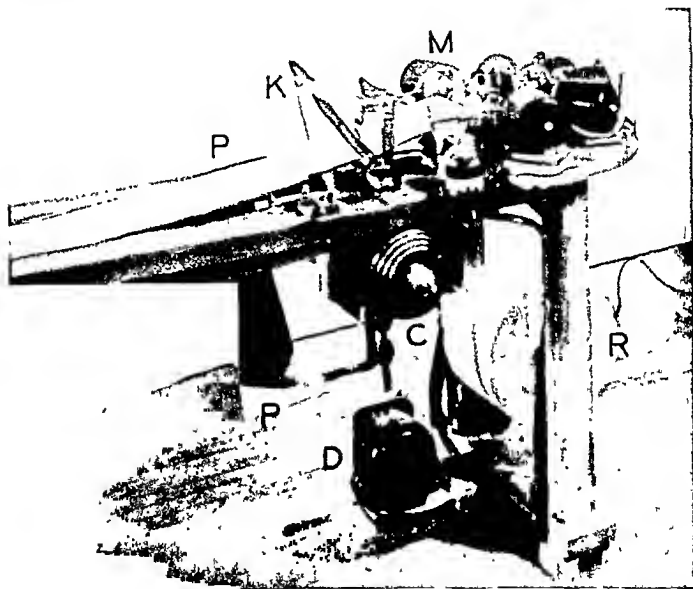


FIG. 2. Paper cutting brain potential recorder showing roll of paper (R) which passes under pens activated by 6 magnets (M) and is cut by a knife (K) each 30 seconds, turned over and laid on a pile (P). The machine is driven by synchronous motor, D. The contact wheels, C, are so arranged that stimuli can be sent to the subject at predetermined times.

The amplifying system is fundamentally similar to that described in 1937, a four-stage push-pull type with special low noise tubes (1603) in the first stage. An additional power stage drives specially constructed dynamic ink writers. So many inquiries have been made regarding the amplifiers that a complete diagram with all details is given in Fig. 1. The new set contains an important improvement which prevents "in phase" potentials, (i.e., those that reach the two grids simultaneously) from being amplified. As a result the subject does not have to be "grounded" at any point and potentials from the heart do not interfere even if one amplifier is attached to leads from an arm while others are attached to

leads from the head. The chief advantage is that the problem of shielding the subject from stray fields is greatly reduced. This result is accomplished by using large cathode resistors connected to negative potentials in the first three stages. Frequency response is practically uniform over the range 0.3 to 46 cycles. Pen deflection is proportional to microvolt input up to a point where neon lamp limitors prevent excessive movement of the pens.

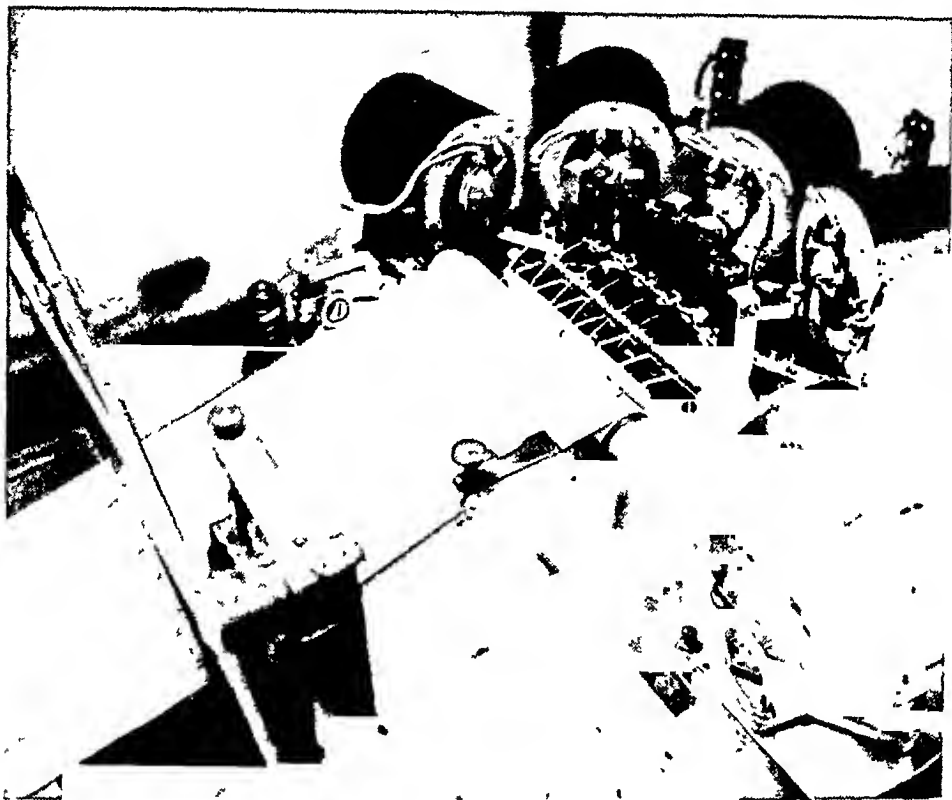


FIG. 3. Enlarged view of electromagnets and 13 pens which write on paper. The flying shears are clearly shown.

The six dynamic pens are arranged in a semi-circle about a moving strip of paper, coming from a roll, seven inches wide. When 30 seconds (1 second = 3 cm.) of recording has occurred the paper is automatically numbered and cut by a moving knife, turned over and placed in position on the previous sheets ready to be bound together for permanent keeping. The recording machine, which has nine different speeds, is shown in Fig. 2 and the electromagnetic ink writers in Fig. 3. Alternating with the six dynamic pens are seven additional pens actuated by small electromagnets. One is a signal pen to record stimuli; the other six record from circuits tuned to any desired frequencies. The appearance of the tuned channels is shown in the records between the brain potential lines. They supplement the untuned record and make it possible to give an accurate figure for the "alpha index" or the index of any other frequency of interest.

#### DISTRIBUTION OF POTENTIAL PATTERN

Before considering the effect of stimuli, a general picture of the cortical distribution of potential pattern is necessary. We are again impressed with the similarity of records from the same person on different days. Because of

the variation in pattern from person to person it is only possible to make the most general statements; in fact every generalization has its exceptions. Any part of the head connected with any other part will give rhythmic potential differences. The nearer the electrodes, the less the amplitude of potentials and if the two are brought very close together (15 mm.) high amplification is necessary to detect them. As stated previously this means that the two regions must be changing in potential simultaneously and chiefly in phase, as can be proven by comparing each of them with the ears. By such a method of study it is commonly observed that very large regions of the cortex may change in potential simultaneously.

In any one person of the dominant alpha type (see Davis and Davis, 1936) the relative average amplitude of alpha potentials occurring simultaneously in back, top, and front regions may occur in such ratios as 100:60:40 or 60:40:40 or 60:50:0. These figures, given above in  $\mu$  V, might be continued indefinitely by a careful study of different persons.\* Rarely the frontal alphas are larger than the occipital.

If five electrodes are placed on the mid-line in positions 2, 3, 4, 5 and 6, Fig. 4, the recorded amplitudes of simultaneous alpha potentials compared with the left mastoid (7), are shown in Table 1. Note in this particular case, the average values in  $\mu$  V from front to back are 42, 51, 64, 81, 33. The last value of 33 on electrode 6 is from a point below theinion. The table also shows

Table 1. Amplitude of alpha rhythm.

Electrodes on midline of head front to back in positions illustrated in Fig. 4 are compared simultaneously at times chosen at random over a period of 10 minutes.

Electrode position	Amplitude in microvolts										Average
Front. 7-2	40	50	40	50	40	40	30 <sup>1</sup>	40	40	60	43
7-3	50	60	50	50	40	50	40 <sup>1</sup>	50	40	70	50
7-4	70	80	60	60	60	70	40	50	80	70	64
7-5	100	100	90	90	100	80	90	100	80	70	90
Back. 7-6	50	30	40	30	20	30	60	40	40 <sup>1</sup>	20	36

Electrode position	Amplitude in microvolts										Average
Front. 7-2	20 <sup>1</sup>	30	60	40	20	20	50	50	70	60	42
7-3	20 <sup>1</sup>	40	70	50	30	40	80	50	70	70	52
7-4	30	50	80	70	40	50	90	60	70	100	64
7-5	120	80	50	100	60	80	70	100	40	30 <sup>1</sup>	73
Back. 7-6	50	40	20	40	30	40	20	30	30 <sup>1</sup>	10 <sup>1</sup>	31

<sup>1</sup> Out of phase.

that the potentials are almost always in phase (occasionally out of phase in front and in far back) and that the distribution varies from time to time, al-

\* Since this paper went to press an interesting study has appeared of alpha rhythm distribution by M. A. Rubin (*J. Neurophysiol.* 1: 313-324, 1938.)



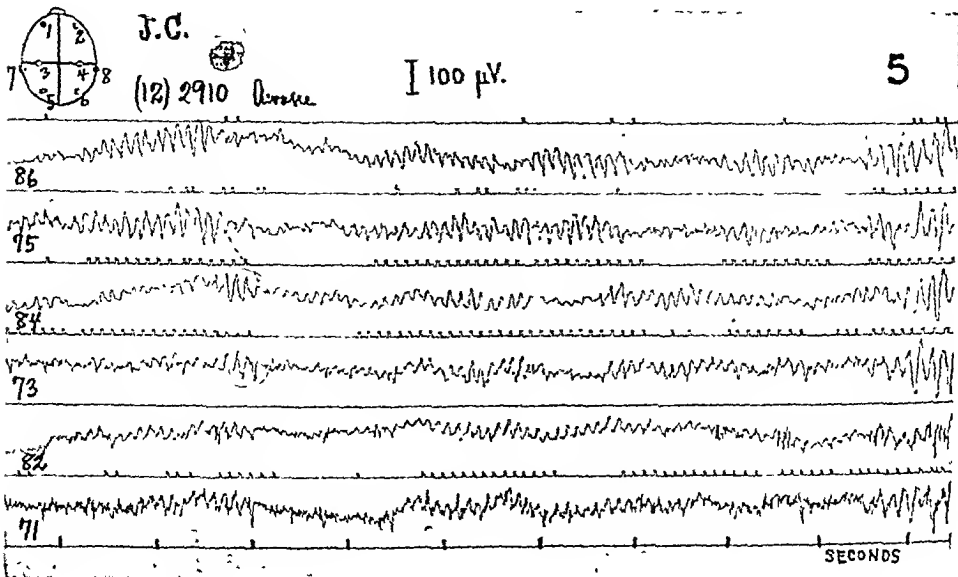
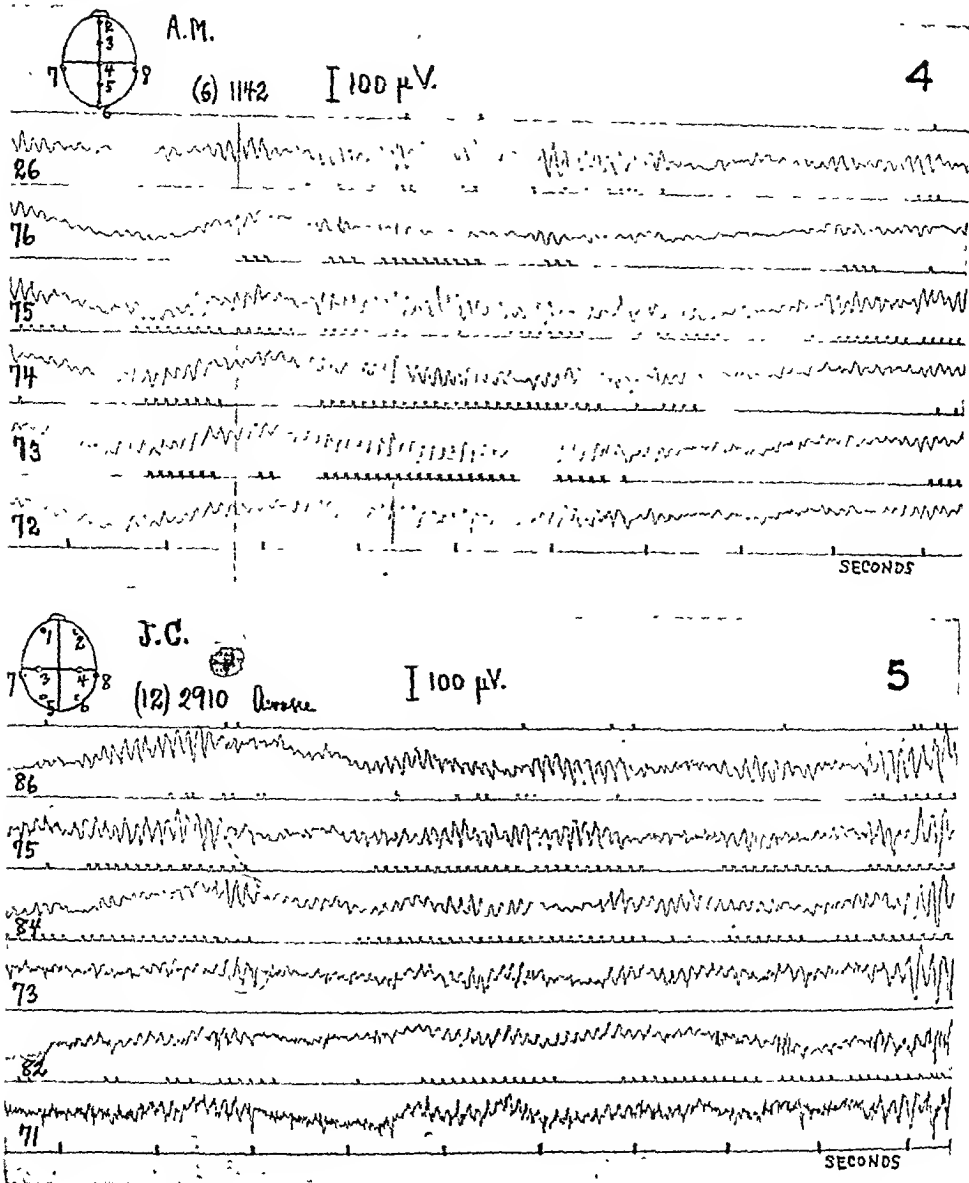


FIG. 4. Alpha type, awake. In all figures the numbers at left indicate placements of electrodes, looking down on head from above as in diagram. Seven and eight are the left and right mastoid bones. When first indicated position is positive the pen moves down. The lines between brain potential records give tuned frequencies. Note that interruptions affect alpha rhythm over whole of head but are more marked in some regions than in others. At the first vertical line 4, 5 and 6 are in phase 2 and 3 out of phase; at the second vertical line all regions of the head are in phase.

FIG. 5. Alpha type, awake. Note that modulation of alpha rhythm usually occurs over whole of head but may appear first on back then on top (in left circle) or may affect back but not top (in right circle). At extreme right note large ( $130 \mu V$ ) 8 per second waves appearing in all regions. Beta potentials are superposed on the alpha in the front regions.

though the occiput almost always leads in amplitude. This is a frequent picture of alpha distribution, shown in Fig. 4. We have here an excellent example of the dominant alpha type with potential over the whole head changing together, first positive then negative with respect to the ears, ten times a second. The amplitude varies from place to place but the well known interruptions or modulation of the alpha rhythm commonly occur over the head as a whole, only rarely appearing locally in one particular region. Examples of such local distribution are shown within the circles of Fig. 5. In rare cases, large eight-per second potentials may appear simultaneously in all regions, such as those at the right margin of Fig. 5.

In the low alpha type, frequencies are so irregular that a general statement of distribution is difficult. Such a record is shown in Fig. 6. During sleep the alpha rhythm may appear simultaneously in all regions as a result of a tone stimulus. This is shown in Fig. 7, of the same subject. Our observations agree with those of Berger (1933) and with Jasper and Andrews (1936, 1938) that right and left sides show similar patterns; front and back often different ones; also that the beta rhythm, when it appears, is predominantly front and top while the alpha rhythm is predominantly back and top.

#### STIMULI AND DISTURBANCES

By a "disturbance" we refer to any marked change in the regularly occurring potential pattern. These may be spontaneous or they may be the result of external stimuli. No doubt the spontaneous disturbances come from internal stimuli of one kind or another. Thus, when awake, modulation of the alpha rhythm merging into longer interruptions, as already pointed out, *generally* affects, simultaneously, all regions in which alpha rhythm appears. Suppression of the alpha rhythm by light likewise occurs simultaneously in all regions, with occasional exceptions. Jasper and Andrews (1938) have observed light to suppress the occipital alpha but not the frontal alpha rhythm. They also observed the frequency of the two to be different. Occasionally light has little effect on the alpha rhythm, as shown in Fig. 8, where there is only a transitory suppression in all areas.

Davis, Davis, Loomis, Harvey and Hobart (1938) observed in the drowsing state that the alpha rhythm sometimes disappeared on back but not on top during the momentary loss of consciousness experienced at the onset of sleep. However, in looking over a large number of records taken from six different regions of the head simultaneously, one is impressed with the widespread simultaneous changes in widely separated areas, rather than with local differences.

It is in sleep that the most interesting and varied changes in potential pattern occur as a result of stimuli. These were first noted by Loomis, Harvey and Hobart (1935, 1936) and have been observed by Blake and Gerard (1937) in their interesting study of the relation between potential pattern and depth of sleep. Loomis, Harvey and Hobart (1937) have described five successive changes in brain potential pattern representing stages or states of sleep that

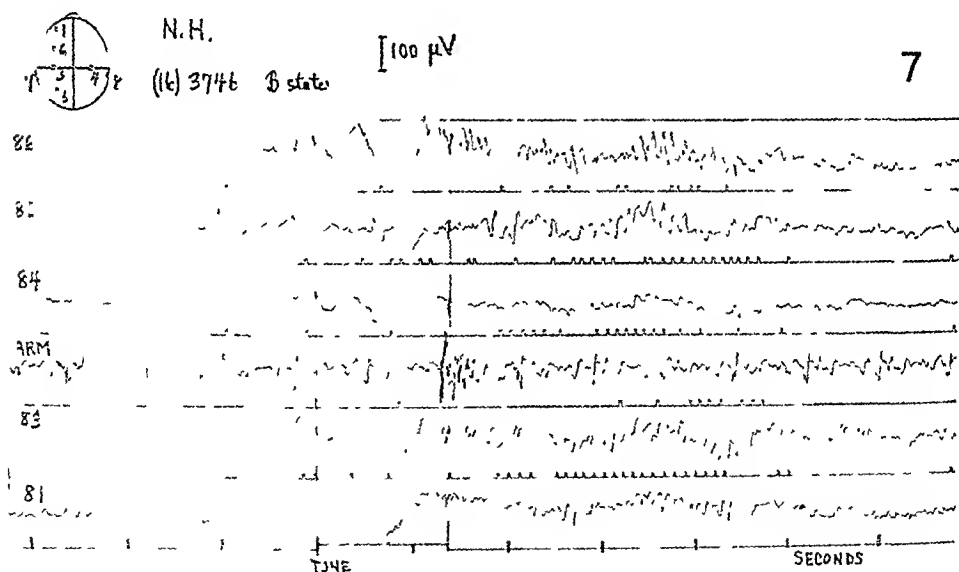
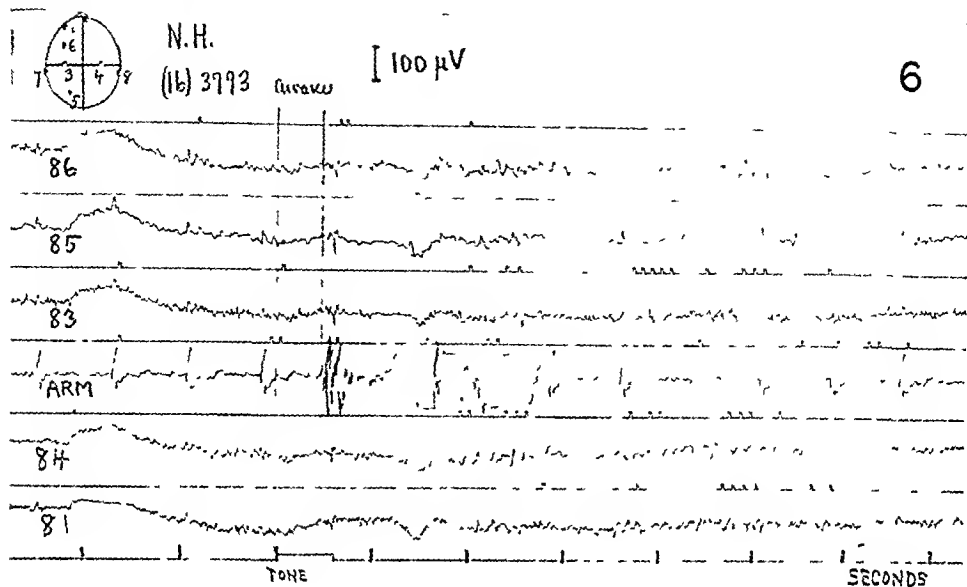


FIG. 6. Low alpha type, awake. Note irregular potentials with beta rhythms on top and front. Electrocardiogram shows on arm electrodes, which also indicate muscle potentials after a tone signal, giving reaction time.

FIG. 7. Same subject as Fig. 6 in B state of sleep; 84 at half amplification. Note long reaction time, indications of a K complex and simultaneous alpha rhythm following a tone stimulus.

are very well defined. These are designated A, B, C, D, and E. During the night a sleeper continually shifts back and forth from one state to another, either spontaneously or as the result of stimuli. The patterns are shown in Fig.

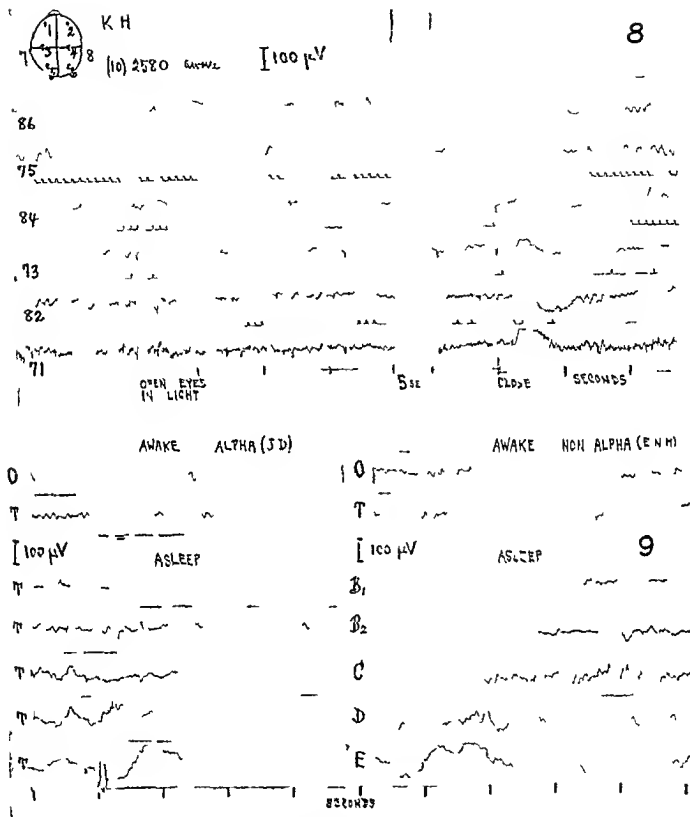


FIG 8 Alpha type showing partial suppression of alpha rhythm by light. Note potentials due to eyeball movements when eyes are closed.

FIG 9 Brain potential activity in an alpha type of person and a low alpha type awake and asleep. O = occipital region, T = top of head. B<sub>1</sub>, B<sub>2</sub>, C, D, and E refer to states of sleep. Note that when asleep the patterns are much more alike than when awake.

9 Our present work, based on 25 afternoon naps of 10 persons, has completely confirmed the previous experiments and made it possible to state more definitely the distribution over the head of 14 per second "spindles," four to five per second waves, and the large delta potentials. The E state is rarely

reached in an afternoon nap. A very characteristic response which we call the K wave or complex appears in some states of sleep, either spontaneously or as the result of stimulation.

Records of persons which are quite dissimilar when awake, become much alike when asleep. The drowsing state A, with intermittent alpha rhythm, studied in detail by Davis, Davis, Loomis, Harvey and Hobart (1937) reflects the pattern when awake but states B, C, D, and E are fundamentally alike in the alpha and the non-alpha types of individual. This is illustrated in Fig. 9. In the B or low voltage state potential change is of low amplitude over the whole head. When four to five per sec. waves appear, they are largest on the top, then on the front and then on the back. In the C or spindle state the amplitude of spindles is usually largest on the top. They may also be prominent on front or back in some persons. Such a distribution is shown in Fig. 13. In the D state, spindles continue to come from the same regions, while the large random or delta waves of one a second come from all parts of the head. They are largest from the top, less large from the front, and smallest from the back. In the E state, where the spindles become inconspicuous, the delta waves continue from all parts of the head with the same relative distribution in size.

The ability of a subject to respond to a stimulus as he falls asleep was tested as follows. At predetermined times, most often at half minute intervals, stimuli were automatically sent to the sleeper, who was asked to squeeze a bulb in his right hand if he heard a sound (tone from loud speaker) or noticed a light (incandescent lamp, bright enough to be detected through closed eyelids) or felt a weak intermittent induced electric shock applied to his left little finger. Squeezing the bulb made a contact, activating a signal magnet which marked the record. Electrodes on the right forearm also recorded action potentials from muscles involved in squeezing the bulb.

At first, when the subject is still awake, a tone stimulus (not in itself loud or startling) is frequently found to suppress the alpha rhythm if the subject has been asked to react by squeezing the bulb. The phenomenon is illustrated in Fig. 10 where the tone occurs just as a train of alpha waves begins. It will be noted that the alpha rhythm disappears in all regions simultaneously. Many observers have described an effect ("startle effect") when the subject was suddenly "startled," as by a loud unexpected voice, and an unexpected touch, etc. There results also a momentary suppression or practically all electrical activity for a short period (one-half to several seconds).

It is likely that the essential cause of a startle effect is a stimulus to which the subject feels he should react with a motor response. Jasper and Cruikshank (1937) have spoken of the "signal value" or "arousal value" of the stimulus. Thus, a faint tone repeated every 30 seconds does not suppress alpha rhythm but if the subject is told to squeeze a bulb whenever he hears the tone, the effect is marked.

With one subject, ten successive trials gave the suppressions illustrated in Table 2. We wish to emphasize that when this effect occurs it is observed over all regions of the head at the same time. Regularly during the B state of sleep and sometimes during the C state, tone, light or electrical stimuli would give

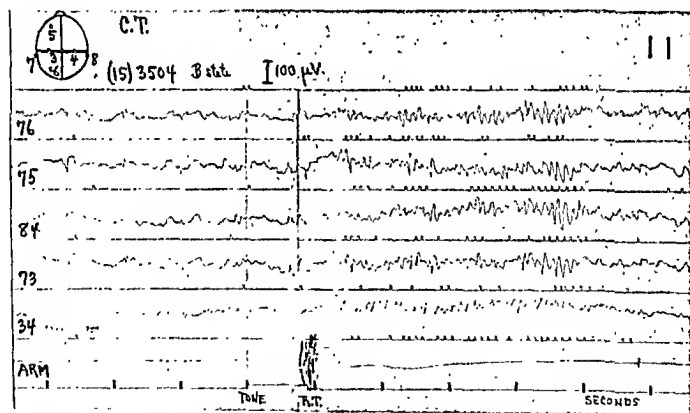
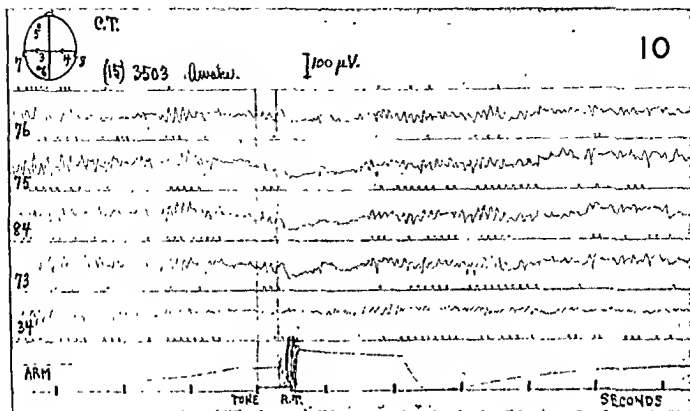


FIG. 10. Alpha type responding to a tone signal by squeezing bulb in right hand which turns off tone, recorded on lower line. Electrodes on right forearm record muscle potential (ARM); 34 records difference in potential of right and left hemisphere over motor region. Note reaction time about 0.3 second. Alpha rhythm which has just started is suppressed simultaneously.

FIG. 11.  
time 0.75 sec  
and then disappears simultaneously.

in all regions.  
e min. later, in B state of sleep. Note reaction  
alpha rhythm appears on all parts of the head

rise to the short bursts of alpha rhythm previously described. Alpha rhythm usually came from all regions of the head which characteristically produce alpha rhythm in the particular person being studied. The rhythm began simultaneously and ended simultaneously in the different regions. A marked effect of this type is shown in Fig. 11. Tone and light were more likely to arouse alpha rhythm than electrical stimulation. If the stimuli were sent in at half minute intervals the subject became accustomed to them and failed to respond by the appearance of alpha rhythm, the adaptation being most marked in the case of electric stimulation of the finger. A change in frequency or intensity (even lowered intensity) of tone or intensity of light or tickle would again start alpha rhythm from large areas of the head simultaneously. Frequently the alpha rhythm began as the stimulus ceased.

Table 2

Suppression of alpha rhythm after ten successive tone stimuli, when the subject was asked to respond by moving hand. The figures give time in seconds.

Trial	1	2	3	4	5	6	7	8	9	10	Average
Reaction time	.23	.23	.20	.27	.20	.20	.23	.27	.33	.37	.25
Time of beginning of suppression	.33	.33	.66	1.1	.33	.33	.36	.40	.46	.50	.48
Duration of suppression	.60	.53	1.6	.33	.33	.36	1.6	.36	1.5	.33	.75

This appearance of alpha rhythm over all areas is obviously a shift of the person from one level to another, from the B to the A state of sleep, and not any "evoked" effect of the stimulus, as such. It is the widespread distribution that is notable. The response to light is particularly important and interesting since light abolishes the alpha rhythm when awake and yet gives rise to the rhythm when asleep. The change in reaction time is quite interesting as the subject drops off to sleep. Figs. 10 to 13 show how this gradually lengthens as the character of the brain potentials changes, often becoming over a second in length. We have regularly observed this correlation. Sometimes abortive attempts to squeeze the bulb appear in the record of arm muscle potential without an actual contact being made, as shown in Fig. 13. In the transition between the B and C states of sleep the change in potential pattern occurs over all regions of the head.

When the C state of sleep is reached an interesting and characteristic large potential change occurs as a result of tone stimulation which can be designated a K wave or K complex. This starts in the late B state and appears in the record as a swing down (sometimes up and then down) and then up, corresponding to a negativity (pen moves down) and then a positivity (pen moves up) of the head with respect to ears. It is shown in Figs. 12, 13 and 14. The beginning of a K complex appears in Fig. 7.

The actual potential change may be as high as 200 to 300 $\mu$  V and the period about a second. The maximum positivity occurs about 0.75 second after the

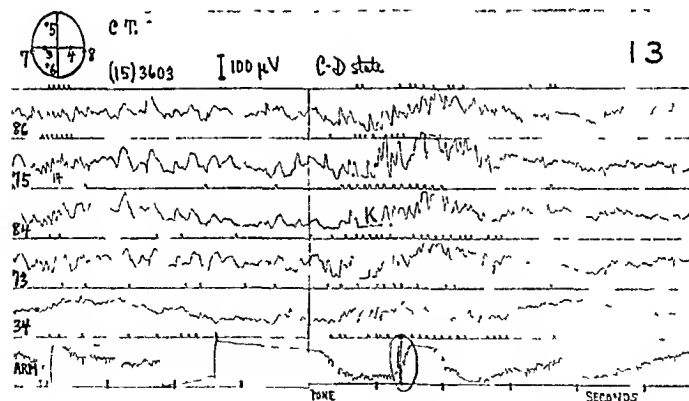
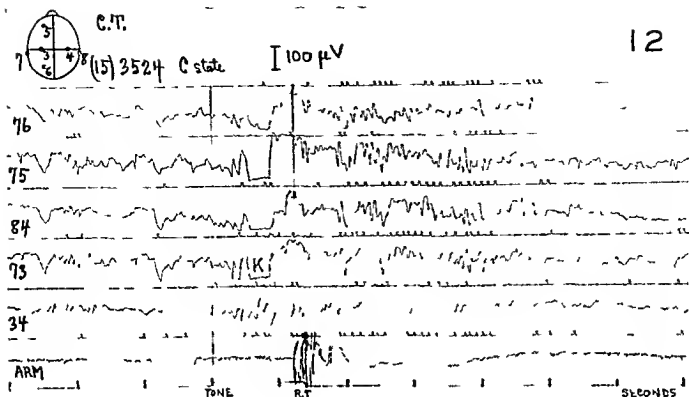


FIG 12 Same subject as Fig 10, 10 min later, in C state of sleep. Note reaction time now 1.25 seconds and the appearance of the K complex, a large slow potential change in which the head becomes negative and then positive to ears, followed by several large potential changes with higher frequency superposed.

FIG. 13 Same subject as Fig. 10, 50 min later, showing attempts to squeeze bulb not rewarded with success. At left note 14 per sec rhythm widely distributed over head, followed by 4 per sec waves and a slight K wave, as a result of the tone stimulus.

tone stimulus begins. With increasing positivity of head there are superposed waves of fourteen to eight per second, rather irregular in frequency. Sometimes there will be several large negative and positive swings in succession resem-





has received no tone stimulus. Sometimes it has been observed to be coincident with a feeble attempt of the sleeping subject to squeeze the bulb, before the stimulus, as shown in Fig. 14. It has appeared in all our regular subjects and is most prominent on top, less on front and least on back of head.

The interpretation of these K waves is difficult and demands further investigation. They are clearly not electrical artifacts nor are they due to movements of the eye balls, as they are larger on the top than on the front of the head. The form is also different. They are not due to movements of head wires as they do not show on electrodes placed over corresponding parts of the right and left hemispheres. Since they have about the same amplitude and period as delta waves, they may perhaps be regarded as the forerunner of these large potentials characteristic of the D and E states of sleep. The K wave is not the only type of disturbance that occurs in the C state. Fig. 15 shows an unusual sudden change from spindles to 8 per sec. rhythm not correlated with any external stimulation. Note that it extends over a considerable area, begins and disappears simultaneously and lasts three seconds. Since the record of this person awake was also unusual we may regard it as decidedly atypical.

The general picture of the cortex that we form from the preceding study of disturbances is of an organ whose parts are so intimately connected that it is unusual to find a disturbance of spontaneous rhythms that is confined to local areas, and almost never confined to a single convolution. When the whole head is "beating" in phase with a frequency of 10 per sec. in different regions, the question arises as to what the relation to individual neurons can possibly be. How can we conceive of a regular pattern which extends from forehead to occiput arising from several layers of cells which are themselves oriented by the complex folding of the cortex? The answer must come from animal experimentation.

#### SUMMARY

A study has been made of potential pattern from six different regions of the human cortex recorded simultaneously. Combined with the findings of numerous other investigators of human electroencephalography we obtain the following general picture of potential distribution. Right and left halves are fundamentally alike in pattern while front, top and back may be quite different. Beta rhythm is predominantly front and top while alpha rhythm is predominantly back and top. Very large areas exhibit the same pattern or frequency which is often synchronous and in phase, less often out of phase and of slightly different frequency. Amplitude may vary greatly in different regions and at different times. Exceptions have been noted to all the above statements.

In the A (drowsing) state of sleep, patterns reflect those of the person awake but in the B, C, D and E states all persons show fundamentally similar patterns, fourteen per sec. rhythm appearing predominantly on top and large delta waves over the whole of the head.

A disturbance affecting alpha rhythm when awake usually involves simul-

taneously all areas showing alpha rhythm, with delay of appearance in certain regions occasionally observed.

A disturbance during sleep, whether resulting in the return of alpha rhythm, or the appearance of large seven-per-second potentials, or of the newly described large K waves, affects all regions of the head to some extent. The K wave or complex is most marked in the C state of sleep, appearing as a negative and then a positive swing (with respect to ears), with superposed 14 to 8 per sec. rhythm. It regularly results from a tone stimulus but may appear spontaneously, most marked on top, less on front and least on back of disturbance head.

With respect to disturbance potentials appearing on the surface of the skull the cortex thus acts as a whole.

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# THE FRIGHT REACTION AFTER SECTION OF THE FACIAL, TRIGEMINAL AND CERVICAL SYMPATHETIC NERVES\*

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## INTRODUCTION

IN A previous communication<sup>1</sup> observations on reactions of denervated cranial muscles to fright were described. It was noted that two or three seconds after a monkey (*Macaca mulatta*) had been frightened its denervated facial or ocular muscles showed slow contractions. This contraction, termed the "fright reaction," lasted for 30 to 40 seconds. The reaction could be augmented by eserization and reproduced by parenteral injections of acetylcholin. Injections of adrenalin in small or large quantities failed to produce contractions in the denervated muscles. The contractions produced by fright and acetylcholin were closely parallel in type. They occurred only while the muscles remained denervated. All available data seemed to point to the fact that the fright reaction was due to a humoral agent which in its action on denervated muscles was similar to acetylcholin.

The site of formation and the manner in which the cholinergic substance reaches the denervated muscles are still moot points. It would be possible for the agent to diffuse to the denervated structures from secretion in local tissues or from the blood stream. It is the object of this report to show that the fright reaction is not due to local secretion of acetylcholin. It is well known that electric stimulation of vasodilator nerves causes liberation of acetylcholin at their nerve ending.<sup>2</sup> Such a secretion among denervated muscle fibers would produce in them a slow contraction. Previously in an attempt to eliminate this factor of local diffusion as a possible explanation for the fright reaction the superior cervical ganglion, sympathetic trunk and infraorbital nerves were cut.<sup>1</sup> These procedures did not abolish or materially reduce the contraction associated with fright. Hinsey,<sup>3</sup> however, suggested that the inferior cervical ganglion and uncut portions of the trigeminal nerve might be involved in the local production of acetylcholin within the facial or ocular muscles. There are also other nerves in the regions denervated which may act as a source of local secretion of the parasympathetic substance. To insure complete interruption of the local nerve supply to the face and eye the oculomotor and trigeminal nerves were cut intracranially, while the facial, chorda tympani and part of the pharyngeal plexus, were cut extracranially. In addition the superior middle and inferior cervical ganglia were removed and the carotid artery was denuded.

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## RESULTS

*Section of facial nerve*

In most instances the facial nerve was cut at the exit of the stylomastoid foramen. The fright reaction in the denervated facial muscles appeared 7 to 10 days after nerve section, irrespective of what part or to what extent the nerve was excised. Intracranial or intracanalicular resection, avulsion of the geniculate ganglion, or excision of all branches of the facial nerve yielded identical results. In every instance a typical peripheral facial paralysis with loss of electrical reactions appeared. In some monkeys the skin temperature of the denervated face and ear became warmer, but later grew cooler than the normal side. So long as the muscles remained denervated the fright reaction could be elicited. The sensitivity to acetylcholin reached its maximum about 25 days after the nerve section. Thereafter, with regeneration of the nerve, it diminished unless the heightened sensitivity was maintained by periodic resection of the nerve fibers.

*Section of the oculomotor and trigeminal nerves*

The technique for section of the oculomotor and trigeminal nerves was the same. Only observations on trigeminal nerve section will be described here as the results of oculomotor nerve section have been reported already.<sup>4</sup> Through a large bone flap the greater, especially the posterior, part of the cerebral hemisphere was uncovered. Such an exposure made it possible to examine cranial nerves III, IV and V. By gently elevating the temporal lobe from its middle fossa, the petrous pyramid and its apex were visualized. Around the cerebral peduncle the trochlear and more anteriorly the oculomotor nerve could be seen. Near its apical insertion the tentorium cerebelli was incised, bringing the trigeminal nerve into view. Two roots were clearly discernible, the smaller being more lateral. Stimulation of these roots caused closing of the jaw, and, with strong enough current, the ipsilateral facial muscles contracted. The latter contractions were abolished immediately after the peripheral facial nerve supply was interrupted. Apparently the abnormal facial contraction obtained on stimulating the trigeminal nerve roots with unipolar and bipolar electrodes was due to electrical spread. Stimulation of the trigeminal nerve more anteriorly in its preganglionic divisions yielded the same responses. Stimulation of the first division caused a dilatation of the pupil and slow retraction of the upper eyelid. The latter responses were similar to those obtained on stimulating the cervical sympathetic, except that there was no piloerection.

The entire trigeminal nerve was cut. In one monkey the incision extended anteriorly to include the Gasserian ganglion. This lesion, in addition to the signs described below, was followed by a herpetic eruption of the skin about the eye. The signs of trigeminal nerve section were: (i) loss of the direct corneal reflex and of sensation over the face; (ii) decrease in pupillary diameter, pseudoptosis and (iii) deviation of the jaw to the ipsilateral side.

The decrease in the pupillary diameter was the result of interruption of

sympathetic fibers running through the trigeminal nerve to the eye. This was verified: (i) by lack of pupillary dilatation after instillation of cocaine (4 per cent) in the conjunctival sac; (ii) by absence of pupillary dilatation but presence of piloerection on stimulating the ipsilateral cervical sympathetic chain; (iii) by marked pupillary dilatation following parenteral injection of adrenalin. The latter is a sensitization phenomenon in the pupillary dilator fibers denervated by the trigeminal nerve section. Lack of piloerection as part of the syndrome of sympathetic paralysis was not seen. These observations indicate that sympathetic fibers to the eye course from the carotid plexus by way of the first division of the trigeminal nerve.

#### *Cervical sympathetic chain*

Stimulation of the cervical sympathetic did not yield any visible contractions in ipsilaterally denervated facial muscles. Eserinization did not alter the situation. There was not the slightest evidence of the Rogowicz phenomenon<sup>5</sup> even at a period when the denervated muscles were most sensitive. Stimulation was carried out under ether or nembutal anesthesia in 6 monkeys; in 3 the stimulus was applied above the middle cervical ganglion, in one at the middle cervical ganglion and in 2 at the inferior cervical ganglion. The duration of the stimulus varied from 5 to 45 secs. and varied in intensity.

Resection of the middle and superior cervical ganglia, with the intervening sympathetic trunk, and of the stellate ganglion by the posterior approach did not affect the fright reaction. Combined section of the ipsilateral trigeminal roots with the entire cervical sympathetic chain still did not inhibit the contractions of the denervated muscles observed in fright or sudden effort. The signs of stellate ganglionectomy in addition to the typical Horner's syndrome were increase of skin temperature, redness and some swelling (vasodilatation), anhidrosis and piloparesis of the hand.

To ensure interruption of all nerves which may possibly exist in the vicinity of the denervated facial muscles the trigeminal, chorda tympani, part of pharyngeal plexus, superior laryngeal, hypoglossal nerves and the entire cervical sympathetic chain were resected and the carotid artery denuded on the side of the facial denervation. In addition the vagus nerve was avulsed from the jugular foramen while the spinal accessory nerve was crushed. These procedures, carried out in several stages on the same monkey, were without influence on the fright reaction.\*

\* The following operations were carried out in one of the monkeys (Ptois series No 28): (i) Dec 15, 1937, Section of left trigeminal nerve in middle fossa, (ii) Dec 22, 1937, Resection and crushing of left facial nerve trunk Dec 27, 1937, First appearance of the fright reaction in the denervated facial muscles, (iii) Jan 6, 1938, Stimulation and resection of the left stellate ganglion, (iv) Jan 13, 1938, Resection of left facial nerve scar and branches together with resection of left superior cervical ganglion and the greater part of the sympathetic trunk, carotid denudation, and resection of superior laryngeal nerve, (v) Feb 23, 1938, Resection of the left facial nerve scar with stimulation and resection of left hypoglossal nerve, stimulation and avulsion of the vagus nerve trunk from jugular foramen, section of chorda tympani and branches of glossopharyngeal plexus, crushing and section of branches of glossopharyngeal and apical accessory nerves, ligation and section of external maxillary artery; and finally (vi), Apr 1938, resection of left facial nerve scar tissue

The fright reaction could be obtained at all times so long as the muscles remained denervated. The *facial muscles* were kept denervated by repeated section of possibly regenerated nerves. The facial paralysis was always evident. Electrical reactions of the facial muscles were absent. The signs of trigeminal nerve section persisted for months and were manifest by corneal analgesia with areflexia, analgesia of the face and deviation of the jaw to the ipsilateral side.

The signs of cervical sympathetic paralysis were myosis, enophthalmos, pseudoptosis, anhidrosis, piloparesis, dilatation of the angular vein; increased skin temperature with redness, swelling, and anhidrosis of the hand also persisting for many months. In addition all these denervated sympathetic structures were found to be hypersensitive to adrenalin. The evidence for denervation of the tongue and trapezius muscles was found in their responsiveness to parenteral injections of acetylcholin. The chief sign of vagus nerve resection was hoarseness. Thus with all these cranial and cervical sympathetic nerves destroyed contractions in the paralyzed facial muscles could still be obtained after fright. At no time was there observed any reduction in degree of these fright contractions.

#### DISCUSSION

The foregoing experiments indicate that the contractions in denervated muscles induced by fright or sudden effort are due to a chemical agent, and, unless one accepts the theory that the autonomic system is a syncytium,<sup>6</sup> the source of the chemical substance is not regional. The substance is formed not only locally but throughout the body. Under conditions of strong emotion or sudden effort the entire nervous system is vigorously activated. At the nerve endings acetylcholin may be formed in amounts larger than usual. A portion of the excess of the cholinergic agent, after being absorbed into the general circulation, would then reach and act upon the denervated muscle in question.

The concentration of acetylcholin when absorbed into the blood stream need not be large. In a monkey, weighing 2300 gms., contraction in denervated facial muscles was obtained by the injection into the saphenous vein of 0.2 cc. of a solution of 1:50,000 of acetylcholin in saline. This small amount was effective in causing a minimal visible contraction in the denervated facial muscles in the anesthetized (ether or nembutal), and uneserinized monkey. With eserine the amount of acetylcholin necessary to bring about a minimal contraction was less. After the factors of hydrolysis by the cholin esterase and dilution by the blood stream are taken into consideration, the concentration of acetylcholin reaching the denervated facial muscles must be at least  $1 \times 10^{-8}$  gms. per cc. of blood in non-eserinized and  $1 \times 10^{-9}$  or  $1 \times 10^{-10}$  in the eserinizied monkey. Such sensitivity to acetylcholin is greater than some leech muscles possess. It would appear that the denervated facial muscle of monkeys is a better indicator for acetylcholin than the leech.

Thus far attempts to recover acetylcholin from the blood stream of frightened monkeys have been fruitless. To obtain sufficient volumes of blood

from active monkeys is difficult and to detect such small amounts of acetylcholin even by the eserized leech muscle is a procedure fraught with difficulty.

#### SUMMARY

1. The fright reaction (contractions in denervated facial or ocular muscles induced by fright) was neither abolished nor diminished by resection of combinations of nerves, from the third to the twelfth cranial nerves inclusive, and by simultaneous extirpation of the entire ipsilateral cervical sympathetic chain

2. These findings exclude the possibility that the fright reaction is due to a local secretion of acetylcholin. The effect is probably due to a general secretion of acetylcholin-like substance with secondary diffusion through the blood stream.

3. Intravenous injections of acetylcholin in the uneserized monkey were effective in causing contractions in denervated muscles in concentrations less than  $1 \times 10^{-9}$ . Such small amounts of acetylcholin would be technically difficult to recover from blood.

4. Intracranial section of the trigeminal nerve caused the ipsilateral pupillary dilator fibers to be sensitive to adrenalin.

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# FUNCTIONAL ORGANIZATION IN THE FACE-SUBDIVISION OF THE SENSORY CORTEX OF THE MONKEY (*MACACA MULATTA*)\*

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## INTRODUCTION

ON LOCAL strychninization, *i.e.*, the strychninization of only a few (1-4) square millimeters, of any portion of the cerebral cortex a typical change in the electrocorticogram (ECG) occurs, namely the temporary appearance of large, rapid potential-fluctuations, or "strychnine-spikes." In some regions of the cortex, for instance in the visual cortex, this change remains local, in others the hyperactivity induced by the strychnine does not remain confined to the strychninized locus, but spreads. This is especially conspicuous in the sensorimotor cortex. Upon local strychninization of almost any constituent area of this region of the cortex, strychnine-spikes appear in the ECG not only at the site of strychninization, but over the entire area and even in other areas.<sup>1</sup>

The areal distribution of these spikes differs with each area locally strychninized, thus revealing details of functional organization, *i.e.*, specifically directed functional (and obviously anatomical) relations, in the sensorimotor cortex. The paper just quoted presented the functional organization in the leg- and arm-subdivisions of the sensorimotor cortex; the present paper deals with a similar investigation of the face-subdivision of this region.

## METHODS

All experiments were performed on monkeys (*Macaca mulatta*), fully anaesthetized with Dial;\*\* 0.45 cc. per kilogram bodyweight, half of the dose given intraperitoneally, half of it intramuscularly.

For the electrophysiological and other methodological details the reader is referred to the paper on the functional organization in the leg- and arm-subdivisions in the sensorimotor cortex.<sup>1</sup>

The problem of the placing of the electrodes and the strychnine presents peculiar difficulties in the face-subdivision. The number of areas in this region, especially in its precentral portion, is relatively large. The variability of the macaque's brain is considerable and, finally, worst of all, the boundaries between many of the constituent areas of this subdivision are not indicated by any external landmarks. For want of a cytoarchitectonic map of the macaque's brain, the extent and location of its sensory cortex is given in Fig. 1, in which the areas of the Vogts' map of the cercopitheque's brain (slightly modified) are indicated. It was assumed for this investigation that the cytoarchitecture of the macaque's cortex resembles that of the cercopitheque's brain. The diagram of the Vogts probably represents an "average" picture of their findings in several animals, for they state that their map is based on the study of more than 100 brains of cercopitheque monkeys, but "dass wir uns (aber) in den Abgrenzungen der einzelnen Felder an bestimmte, günstig geschnittene und die Grenzen besonders deutlich zeigende Präparate gehalten haben";<sup>3</sup> (p. 371). Their diagram for the cercopitheque's brain differs in some respects from the macaque's brain, especially in the shape of the arcuate sulcus. This factor and particularly

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\*\* The Dial was kindly put at our disposal by the Ciba Company.

the absence of external landmarks for many of the areal boundaries makes experiments in this region of the cortex of the kind presented in this paper rather difficult. Only analytical comparison of the configuration of the brains and careful correlation of the results of many experiments can help out here.

### RESULTS

For the orientation of the reader with respect to the placing of the electrodes and the strychnine in these experiments the map mentioned in the introduction is given in Fig. 1. Attention should be called to the inclusion of areas L 4-s, A.4-s and F.4-s.

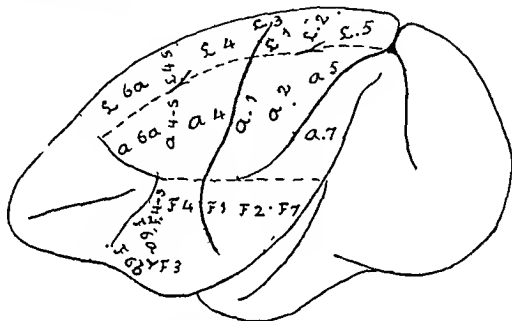


FIG 1 Sensory cortex of *Macaca mulatta* with the architectonic areas (modified) of the map of the cercopitheque's brain after C and O Vogt. The deviations from their diagram are 1 the introduction of the areas L 4 s, A 4-s and F 4 s, 2 the omission of the subdivisions of F 6b, F 3, L 6a and A 6a. It should be noted that these modifications are based upon consideration of physiological, not anatomical evidence.

#### I. *F.6b*.

- a. *F.6b $\beta$* . Local strychninization of *F.6b $\beta$*  "fires" this area, and possibly *F.3*, but not *F.6b $\alpha$* , *F.6a*, *F.4*, *F.1* or *F.2*.
- b. *F.6b $\alpha$* . Attempts to strychninize this area either produced results like those obtained upon strychninization of *F.6b $\beta$*  or those following strychninization of *F.6a* (see below sub II), with "firing" of *F.6b $\alpha$*  in both cases.

#### II. *F.6a*.

Local strychninization of *F.6a* "fires" itself and *F.4* to a less extent (*i.e.* with few and small spikes) and *F.3*, but not *F.6b*, *F.1* or *F.2*.

#### III. *F.4-s*.

Local strychninization of the anterior margin of *F.4* results in a temporary suppression of the electrical activity of *F.4*. (See Fig. 2).

#### IV. *F.4*.

Local strychninization of *F.4* "fires" itself, *F.6a*, *F.1* and to a less extent *F.3*, but not *F.6b* or *F.2*. In Fig. 3 is shown the temporary "firing" of *F.4* and *F.1* following local strychninization of *F.4*.

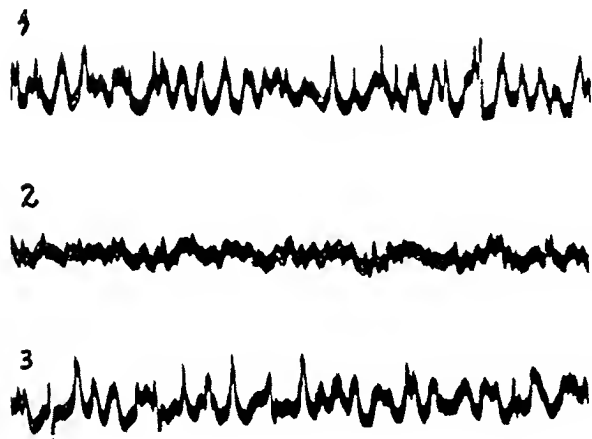


FIG. 2. Shows the temporary suppression of the electrical activity of F.4 following local strychninization of F.4-s. Record 1: before, record 2: at the height of suppression 11 minutes after this strychninization, and record 3: 3 minutes later showing the return of activity.

### V. F.3.

Local strychninization of this area "fires" itself, F.6a and to a less extent F.1, but not F.6b, F.4 or F.2.

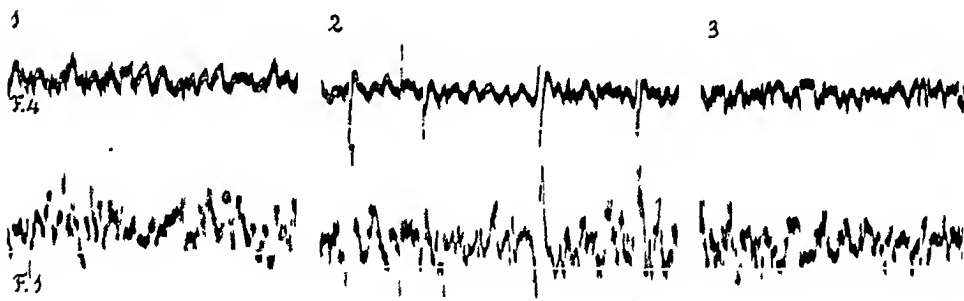


FIG. 3. Shows the temporary firing of F.4 and F.1 following local strychninization of F.4. Record 1: control; record 2: height of "firing" 5 minutes after the strychninization; record 3: return to "normal" 23 minutes later.

### VI. F.1.

Local strychninization of the postcentral portion of F.1 "fires" itself and to a less extent F.6a. It suppresses the activity of F.4 and it fails to "fire" F.6b and F.2. In some experiments a mixed picture of suppression with little spikes appeared in the electrocorticogram of F.4. In one experiment local strychninization of F.1 resulted in a "firing" of F.4 without obvious suppression.

### VII. F.2.

Local strychninization of this area "fires" itself and F.1 (post-central portion), it fails to "fire" F.6b, F.6a, F.4 and F.3.

### VIII. F.7.

Local strychninization of F.7 "fires" itself, F.2 and to a less extent F.1, while it fails to "fire" F.4, F.3, F.6a and F.6b.

## DISCUSSION

Any experimentation requiring differentiation within the face-subdivision of the sensorimotor cortex is difficult for want of external landmarks between its constituent cytoarchitectonic areas. Thus it is impossible to know with certainty beforehand whether the strychninization or the pick-up electrodes are in each case confined to one particular area. Furthermore the individual variation in this subdivision is so great that to know where the areal boundaries are in one animal does not help much in the next. Worst of all is the variation at the triple-point, where F.6a, F.6b and F.3 meet. This point is sometimes, as in the diagram of the Vogts, marked by a shallow dimple, in other animals there is no marking, in still others there is a definite, long anterior subcentral sulcus, usually, but not always, parallel to the fissura centralis. No cytoarchitectonic maps covering all these and other variations exist. Therefore, in each animal several strychninizations and several electrocorticograms from neighbouring loci are required in this region to obtain discrete results, for any one strychninization may be so performed or any pair of electrodes may be so placed as unwittingly to cross a boundary between two areas. Because the local strychninization of each of the three areas meeting at the triple-point results in the firing of a unique group of areas, it is ultimately possible to distinguish the strychninization of any one of these areas from that of any combination of them. Only in the case of area F.6b $\alpha$  have we been unable to apply this diagnostic procedure, for all attempts to strychninize it always resulted in pictures indistinguishable from those which would have been produced if one or the other of the adjacent areas, F.6b $\beta$  or F.6a $\alpha$ , had been involved.

One of the major results in these experiments is that there exists a continuation of the "strip," our L.4-s and A.4-s, into the face-subdivision, i.e., that there exists a F.4-s. This area is a very narrow strip of cortex, 1 to 1.5 mm. wide, 5 to 6 mm. long, lying behind and usually tangent to the upper portion of the inferior ramus of the arcuate sulcus. Its lower end is separated from the arcuate sulcus by a wedge of cortex whose properties resemble those of F.6a (see Fig. 1). In one animal F.4-s nowhere touched the arcuate sulcus, being separated from it by a narrow band of cortex, ca 1.5 mm. wide, which "behaved" like F.6a.

Another striking result in these experiments is the observation that, whereas L.6a and A.6a are not fired by any other area of the leg- and arm-subdivisions, F.6a is fired by F.4, F.3 and to a less extent by F.1. Moreover, whereas strychninization of L.6a or A.6a "fires" the whole of the leg- and arm-subdivision, both pre- and postcentral, the strychninization of F.6a not only "fires" no area outside the face-subdivision, but also fails to "fire" its own postcentral portion and F.6b.

As for F.6b, while not "fired" by any other area, thus resembling L.6a and A.6a, its failure to "fire" any other area, leaves it unique in the sensorimotor cortex. The mixed picture in F.4 obtained upon strychninization of F.1 and the failure of F.2 to "fire" F.4 needs a few words. In the arm- and leg-subdivisions early attempts to strychninize L.1 or A.1 resulted sometimes in

these mixed pictures in L.4 or A.4. We later learned that the mixture was due to trespassing with the strychnine onto area 2. The same explanation may obtain for the experiments on F.1, but it would imply that in several animals (3 out of 6) F.1 was narrower than indicated by the diagram of the Vogts. The one experiment in which strychninization of F.1 resulted in a definite "firing" of F.4 and failed to "fire" F.6a stands alone and must remain unexplained for the present.

One last observation should be mentioned. In several experiments pick-up electrodes were put on F.4, A.4 and L.4 and strychnine applied locally to L.4-s, A.4-s and F.4-s serially. As stated previously, strychninization of L.4-s or A.4-s resulted in a temporary suppression of the activity of L.4 and A.4, without any change in the ECG of F.4. The strychninization of F.4-s not only suppressed the activity of F.4, but also to a less extent that of A.4, while the ECG of L.4 remained unchanged. This finding indicates the existence of a one-way functional relation between F.4-s and A.4. This is of special interest because in all the experiments of this series the "firing" was confined to areas of the subdivision locally strychninized, *i.e.*, to areas of the face-region. Therefore, the suppression of the electrical activity of A.4 upon local strychninization of F.4-s is the only instance in which the functional boundary between the face- and arm-subdivisions of the sensorimotor cortex is not respected. If the suppression from F.4-s like that of L.4-s and A.4-s occurs via subcortical structures and not along cortico-cortical pathways, this transgression of the functional boundary between the face- and arm-subdivisions of the sensorimotor cortex is not a transgression of this functional boundary at the cortical level. This leaves the lack of functional boundary between L.6a and A.6a and L.4-s and A.4-s mentioned previously (1, pp. 73-74 and 82-83) as the only demonstrated hiatus *at the cortical level* in the functional boundaries between the various subdivisions of the sensorimotor cortex.

#### SUMMARY

1. By combination of local strychninization and recording of the electrograms of various areas of the sensorimotor cortex, the functional organization of the face-subdivision of this region was investigated.

2. As previously in the leg- and arm-subdivisions, these experiments revealed directed functional relations between the various constituent areas of the face-subdivision.

3. No "firing" of any area of the arm-subdivision was found upon local strychninization of any area of the face-region.

4. Local strychninization of two areas, namely F.4-s and F.1 (postcentral), temporarily suppressed the electrical activity of F.4.

5. Local strychninization of F.4-s suppressed to a less extent also the electrical activity of A.4. This is the only instance encountered in which strychninization within the face-subdivision produced any change in another subdivision.

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# PATHWAYS THROUGH THE SYMPATHETIC NERVOUS SYSTEM IN THE BULLFROG\*

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PROMPTED by certain difficulties of interpretation in physiological experiments on the splanchnic nerve of the bullfrog (Bishop, 1937), we have undertaken a detailed anatomical survey of the frog sympathetic system. This paper deals with the portion of this system which arises from the first six nerve levels, and includes the supply to the mesentery and gut. The course of each major bundle of pre-ganglionic fibers has been traced, its region of synapse located, and the course of its post-ganglionic fibers determined in general. The methods employed have been dissection, reconstruction from sections of normal and of partially degenerated preparations, and recording of action potentials by means of the oscillograph. Stimulation of nerves in the body has indicated the ultimate destination and function of certain of the pathways recognizable in the sympathetic rami and trunks. Twenty-five bullfrogs have been employed, from which over sixty blocks of tissue have been reconstructed from sections. These include five of the 2nd and 3rd nerve levels, eight of the 4th, eighteen of the 5th, twelve of the 6th, three of the 7th, and ten of the coeliac ganglion region.

From these preparations, an anatomical and functional pattern emerges which, in spite of considerable variability from one animal to another, is rather diagrammatic in its essential relationships (Fig. 1). Considering the most anterior spinal nerve present in the adult as the second segmental nerve, this nerve connects with the sympathetic trunk usually by one or two very fine rami. The 3rd nerve sends one or more rami into it, and receives at least one bundle from it. The 4th nerve sends a ramus anteriorly toward the 3rd, and another posteriorly toward the 5th, and receives two rami from the sympathetic trunk. The 5th nerve contributes two rami, and receives two. The 6th contributes one ramus, chiefly to the posterior sympathetic trunk, and receives one. The 7th nerve contributes one ramus to the trunk, and receives one. Its fibers do not enter the splanchnic nerve, but a strand from the seventh ganglion may pass to the dorsal aorta and kidney.

The pattern is made more obvious when the synaptic regions are taken into account. With a few exceptions to be noted, (i) a ramus passing to the sympathetic does not synapse in the ganglion of that level, but in ganglia anterior and posterior to it; (ii) the rami passing from the sympathetic to the peripheral spinal nerves arise from ganglia at the levels of these respective nerves; (iii) the components of the splanchnic nerve arise mainly from the third to the

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sixth rami, and each synapses partly in the ganglion at the level next below it, and partly in the coeliac ganglion, or even in ganglia more peripheral along the sympathetic nerves.

There are thus two histologically recognizable components from each level: one passing to the peripheral nerves, and one to the viscera. At the 4th level there may be two separate ganglia, one giving rise to the rami passing peripherally in the 4th nerve, the other containing the synapses of 3rd nerve fibers whose post-ganglionic fibers pass into the splanchnic nerve.

The terms "white" and "grey" rami will be employed as usual to designate pre-ganglionic and post-ganglionic connections, respectively, between the spinal nerves and the sympathetic trunk, with the reservation that they cannot be differentiated in the frog by their color. In fact, the "grey" rami of the 3rd to 6th nerves are preponderantly myelinated, while the "white" rami contain many non-myelinated fibers. The histological and physiological results can be correlated through the fact that the myelinated fibers of the sympathetic have a lower threshold and a faster conduction rate than the non-myelinated. They give rise to a *B* wave, and the fastest of these fibers conduct at about 2½ m.p.s. in excised preparations at room temperature. The non-myelinated fibers give rise to a *C* wave, and the fastest of them conduct at about ½ m.p.s. The two potential waves appearing when such fibers are stimulated are well separated after 10 mm. conduction. Besides these two groups of fibers, a variable number of sensory myelinated fibers course through the sympathetic; these conduct more rapidly, and the potential to which they give rise appears ahead of the sympathetic *B* wave, in the position of the  $\gamma$  or  $\delta$  component of the *A* wave of the sciatic.

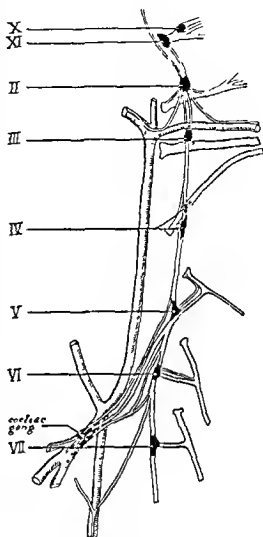


FIG. 1. Schematic diagram of the sympathetic supply to the splanchnic nerve of the bullfrog. Sympathetic chain ganglia numbered II to VII.

#### TECHNIQUE

Bullfrogs were operated under local anaesthesia through a ventral incision to the left of the midline. Either arch of the aorta could be deflected laterally, and after cutting through the dorsal peritoneum, roots were cut by an incision with an iris knife medial to the dorsal root ganglion. Sympathetic trunks and rami were completely severed with scissors. All operations were checked by sections after degeneration from two to five months



were observed after stimulation at various regions. Nerves were then fixed in 10 per cent formol, 5 per cent glacial acetic, stained by osmic acid or silver (usually the Bodian (1936) technique as modified by H. A. Davenport), and cut in 7 to 10 $\mu$  sections. After one or two months, degenerating myelinated fibers are clearly detectable in osmic, but not in silver; that is, the sheaths are altered but the axons are still intact. After about five months, fiber bundles are grossly shrunk and the axons disappear. Reconstruction  $\times 80$  were made of sectioned nerves by counting the serial sections and drawing certain of them in camera lucida. In the figures, areas of ganglion cells are shaded. In making these drawings, the fascicles of complex nerves are represented as lying in a plane, which distorts somewhat their natural relationships.

#### 4TH NERVE LEVEL

The relationships of the 4th nerve level will be discussed first because they illustrate most diagrammatically the courses of typical pathways (Figs.

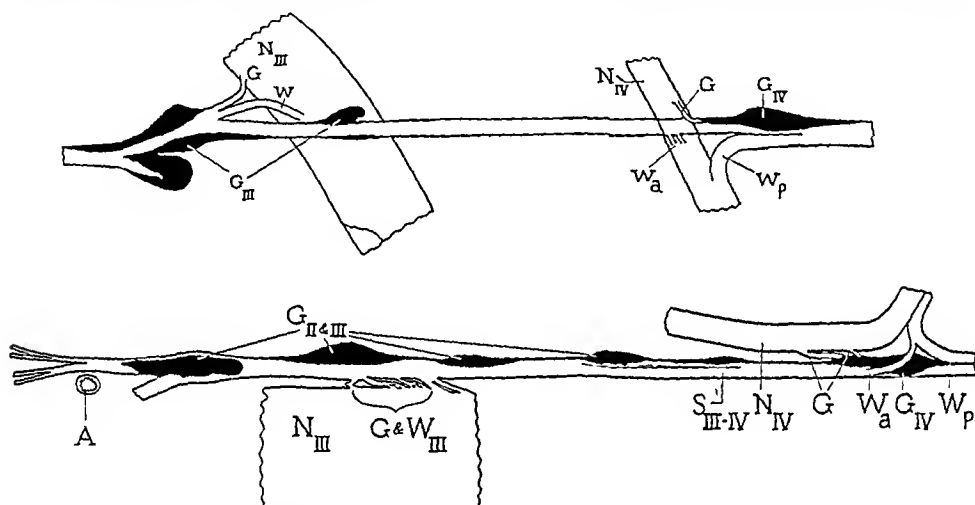


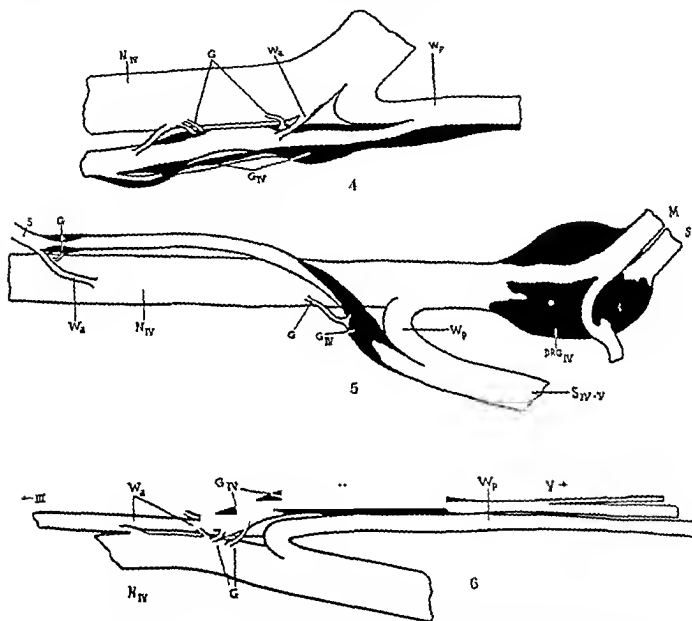
FIG. 2. Reconstruction of 3rd and 4th levels of the sympathetic chain. N, spinal nerve, G, grey ramus, W<sub>a</sub>, white ramus anterior, W<sub>p</sub>, white ramus posterior, G<sub>III</sub> etc., chain ganglia shaded.

FIG. 3. Legends as in 2. Multiple ganglionic masses along sympathetic, and diagrammatic division of 4th white ramus into ascending and descending branches, neither of which terminates at synapses of this level.

2-6). The 4th nerve runs anteriorly and laterally to join the brachial plexus (N<sub>IV</sub>), and is crossed by the sympathetic trunk at an angle of about 30° approximately 3 mm. from the dorsal root ganglion. Posterior to this contact, however, a large white ramus turns caudad from the 4th nerve and joins the sympathetic (W<sub>p</sub>). A triangle is thus formed with the sympathetic as the base and the white ramus and the 4th nerve as two sides. Just anterior to the junction of trunk and ramus, the main 4th sympathetic ganglion lies on the trunk (G<sub>IV</sub>), but no 4th white ramus fibers enter it. Anterior to this, and just posterior to the crossing of the 4th nerve, the two grey rami for the 4th nerve (G) arise from the main sympathetic ganglion or from small separate ganglia. Their post-ganglionic fibers are preponderantly myelinated. At about the same level, one or more white rami pass from the 4th nerve to the sympathetic (W<sub>a</sub>), where they ascend in fiber tracts which pass by the 4th ganglia without

synapses. Thus, few if any white ramus fibers from the 4th level synapse in ganglia at that level, but the grey rami obviously have done so in large part.

The 4th white ramus coursing posteriorly fuses with the trunk from the 3rd level, usually well below the 4th ganglia, to form a single bundle. Some of these 4th white ramus fibers synapse in the 5th ganglion, their post-ganglionic fibers forming the two 5th grey rami. In many preparations, a branch of the



FIGS. 4, 5, 6. 4th sympathetic level. 4 and 5 appear to have separate grey ramus ganglia. In 5, the motor component passes through the dorsal root ganglion and emerges in the white ramus, and a majority of the white ramus fibers synapse in the 4th sympathetic ganglion. In 6, the descending white ramus is separate from the 4th sympathetic ganglion.

sympathetic trunk, containing from one-third to two-thirds of the trunk fibers, the number varying in different preparations, passes the 5th and 6th ganglia entirely in a separate strand, which remains separate until it reaches the region of the coeliac ganglion or, in some preparations, rejoins the main nerve. Some of these fibers are obviously those from the 3rd level which have synapsed in the 4th ganglion; there may be some pre-ganglionic fibers from the 3rd and 4th levels which synapse in the coeliac ganglion. The 4th descend-

ing white ramus ( $W_p$ ) contributes about half the fibers coursing between the 4th and 5th levels.

The 4th ascending white ramus ( $W_a$ ) also consists of two components, one passing to the 3rd nerve grey rami and one to the 2nd and 3rd ganglia, from the former of which several strands supply the head, heart, vessels, etc. In two cases a fine ramus has been found from the 4th nerve parallel to but separate from the sympathetic trunk, ending in a small ganglion, from which two rami entered the 3rd nerve. No other grey rami were found to the 3rd nerves in these preparations, and this fine white ramus contained about one-fourth of the total bulk ascending in the sympathetic from the 4th level. It may be estimated, therefore, that something like three-fourths of the ascending 4th ramus fibers contribute to the supply of the head and heart region. The ascending 4th nerve fibers compose a little less than one-half the total between 3rd and 4th levels.\*

#### II<sup>ND</sup> AND III<sup>RD</sup> NERVE LEVELS

The 2nd nerve usually receives no grey rami from the sympathetic (one preparation has contained a grey ramus), but sends a very fine white ramus from close to its dorsal root ganglion to the 2nd ganglion. The 3rd level sometimes appears to contain no sympathetic ganglion in the frog, but we have found a variable number, from none to four (Figs. 2 and 3), strung along the sympathetic trunk in this region. When no ganglia are present in the immediate vicinity of the 3rd nerve, both white and grey rami pass to the 2nd ganglion, which in this case therefore must represent a fusion of the 2nd ganglion with the 3rd. Contrary to the picture at the 4th level, white rami as well as grey appear always to pass immediately to regions of ganglion cells, and those supplying the head region presumably synapse in the 2nd and 3rd ganglia. Those supplying the posterior regions of the body may also synapse there in part, for the bulk of the sympathetic trunk between 3rd and 4th levels, subtracting the ascending 4th white rami, is still considerably larger than the bulk of the 3rd white ramus. Many of the 3rd nerve fibers, however, synapse in the main 4th ganglion, and stimulation of these causes contraction of the stomach.

#### 5<sup>TH</sup> NERVE LEVEL

The main 5th white ramus (Figs. 7-10,  $W_p$ ) contributes more than one-half the fibers of the splanchnic nerve. Its size is about equal to that of the 5th

\* In this and the following accounts, the statements must be taken generally, for many striking variations are found. For instance, in one preparation with 4th nerve and sympathetic cut anterior to the 4th spinal level, and the 5th white rami cut, there was inappreciable degeneration between 4th and 5th sympathetic ganglia, or even in the stub of nerve anterior to the 4th ganglion. Above the cut the sympathetic trunk to the 3rd level was completely degenerated. Both 4th and 5th sympathetic ganglia were very small, consisting only of scattered cells, and presumably supplied chiefly the grey rami to these levels. In this case no component from above the 4th level passed to the splanchnic nerve; and the sympathetic trunk between 5th and 4th levels, exclusive of the 4th white ramus, must have consisted chiefly of ascending fibers from below the 5th level passing to the 2nd and 3rd levels. The 3rd nerve white ramus passed anteriorly toward the 2nd ganglion, and the 3rd grey ramus was not degenerated, apparently arising from the 3rd sympathetic ganglion.

spinal nerve ( $N_v$ ) with which it forms the 5th trunk. The two grey rami are usually combined with it, but sometimes separate out as individual strands

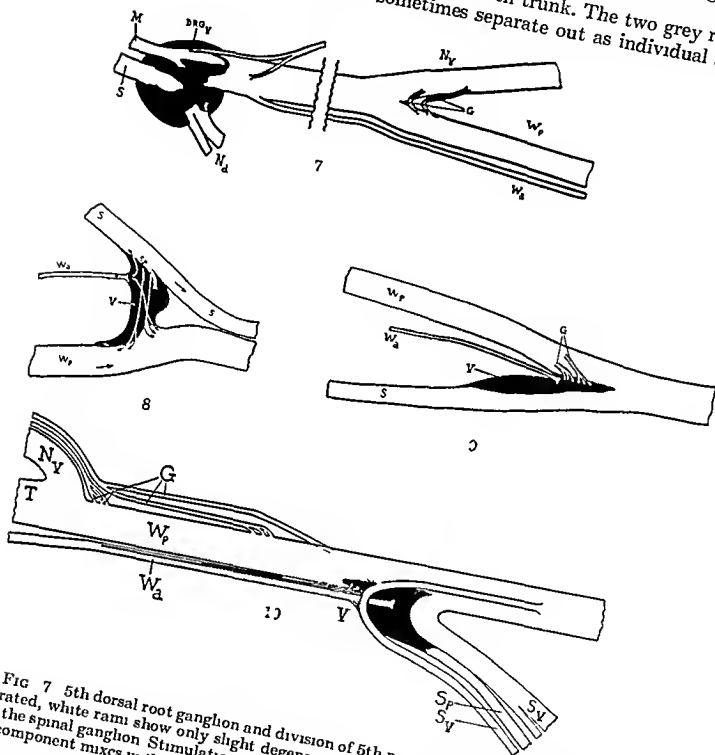


FIG 7 5th dorsal root ganglion and division of 5th nerve and white ramus. Roots degenerated, white rami show only slight degeneration, i.e., the majority of the fibers come from the spinal ganglion. Stimulation of ramus caused gut contraction. Degenerated motor root component mixes with sensory component only below branching of small white ramus  $W_a$ .

FIGS 8, 9, 10 5th sympathetic ganglia, showing relation of sympathetic trunk and white rami  $S_v$ , visceral branch of anterior sympathetic trunk by-passing 5th and 6th ganglia as separate strand to coeliac region in 9, joining trunk again in 10. The 5th nerve and sympathetic trunk in 10 were drawn apart in directions opposite to their normal relations before fixation.

nears its junction with the 5th nerve (Fig. 10). These can always be detected in sections at this crotch by the fact that they are cut longitudinally as they pass from ramus to nerve. They can usually be recognized at the crotch of the

sympathetic ganglion. In two series of sections they have been traced throughout the length of the white ramus, recognizable by a preponderance of myelinated fibers but otherwise appearing merely as two fascicles among the many of which the ramus is composed, without anatomical demarcation from the rest. They arise wholly from the 5th sympathetic ganglion, with their pre-ganglionic fibers wholly in the anterior sympathetic trunk, the stimulation of which produces a *B* wave, but no detectable *C* wave in the 5th nerve (Bishop, 1937). In some osmicated sections, a few structures which stain faintly appear to be non-myelinated fibers, but whether there are more than could be accounted for as sections through nodes of Ranvier has not been determined.

A second fine white ramus separates from the 5th trunk ( $W_a$ ), usually just below the dorsal root ganglion but always above the separation of 5th nerve and ramus. It contains 20 to 40 myelinated fibers, and at least twice that many non-myelinated. It runs parallel to the main white ramus on the side opposite the 5th nerve, and enters the 5th sympathetic ganglion. Its fibers can be traced by stimulation of the 5th trunk after cutting the main white ramus below the point of stimulation. A *B* and a *C* wave then appear in the splanchnic peripheral to the 5th sympathetic ganglion, of a few microvolts each, when the *C* wave produced by stimulation of the uncut larger ramus is  $\frac{1}{2}$  millivolt. A *B* wave only, of some 10 microvolts amplitude, appears also in the anterior sympathetic trunk. No conduction takes place in the reverse direction, or a much smaller *C* wave may appear. The amplitudes of the post-ganglionic waves recorded are such as to indicate that each pre-ganglionic fiber in this ramus must synapse with a number of post-ganglionic neurons. No detectable effect on the musculature of intestine or mesenteric vessels has been observed from stimulation of these fibers, in preparations where stimulation of the main 5th white ramus caused massive contraction of stomach and gut and stoppage of flow through mesenteric vessels. The destination of the fibers ascending in the anterior sympathetic trunk is partly to the 3rd, partly to the 4th grey rami.

The sympathetic often divides just anterior to the 5th sympathetic ganglion (Figs. 7 and 10), and then one branch only enters the ganglion. The ganglion is variable in size, and in some cases its cells would seem to be sufficient in number only to supply the two components shown to synapse there, the fine 5th white ramus and the anterior sympathetic pre-ganglionic fibers for the 5th grey rami. In other cases, a larger ganglion must contain synapses of anterior sympathetic fibers whose post-ganglionics course in the splanchnic nerve and posterior sympathetic trunk. When the sympathetic divides above the ganglion, the strand which joins the 5th rami at this ganglion varies in size with the size of the ganglion. The splanchnic components from the 5th ganglion and white ramus form a single trunk, in which, however, most of the main white ramus fibers from the 5th level can be followed past the ganglion without passing through regions containing ganglion cells. When there is a separate strand from the anterior sympathetic past the 5th ganglion, it may

not fuse with this trunk, although it may have minor anastomoses with it; but few if any of the fibers which have by-passed the 5th ganglion enter the 6th ganglion or posterior sympathetic trunk.

Below the 5th sympathetic ganglion, then, the splanchnic-sympathetic consists typically of two strands (Figs. 7, 11 and 12); if the anterior sympathetic has not divided above the 5th ganglion, a corresponding division takes

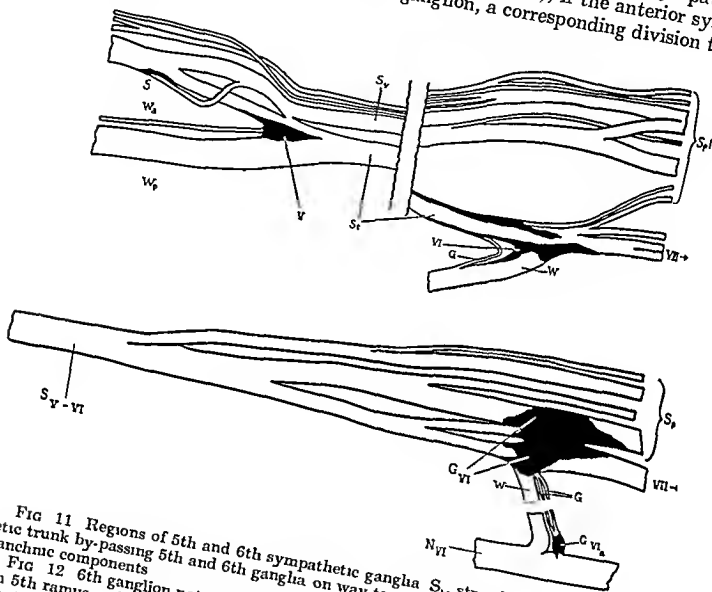


FIG 11 Regions of 5th and 6th sympathetic ganglia  $S_v$ , strand of anterior sympathetic trunk by-passing 5th and 6th ganglia on way to coeliac.  $S_p$ , sympathetic trunk.  $S_{p1}$  splanchnic components

FIG 12 6th ganglion not only on sympathetic trunk, but also on strand that passes from 5th ramus and ganglion to splanchnic. It presumably represents a functional component of the coeliac ganglion,  $G_{VI}$ , is a separate grey ramus ganglion at the junction of grey ramus and 6th nerve instead of at the usual position on the sympathetic trunk.

place just below it, and one strand carries chiefly anterior sympathetic fibers to the viscera. The remaining anterior sympathetic-5th white ramus bundle further separates into three main parts, each of which may divide into smaller strands, to form a plexus. The largest component passes to the coeliac ganglion. The smallest fascicle also passes to this ganglion, and may receive a fine strand from below the 6th ganglion, which then must carry the only contribution from the 6th ramus to the splanchnic. The middle-sized strand runs to the 6th ganglion, beyond which it divides further into two parts.

The larger of these is the posterior sympathetic trunk, the smaller passes along the dorsal aorta and probably supplies the kidney but not the gut, except in those cases where a strand is given off, as mentioned above, to the smaller of the splanchnic divisions. This strand, from the 6th ganglion region to the splanchnic, is relatively much larger in the greenfrog than in the bullfrog.

#### 6TH NERVE LEVEL

The 6th level has two rami, one grey and one white, often fused to a common bundle (Figs. 11 and 12). In one case two ganglionic masses corresponded to the junctions of these two rami with the sympathetic, in which case one was presumably a distinct grey ramus ganglion (see 4th ganglion, above). In another case, a fine ramus passed from near the 6th sympathetic ganglion to a small grey ramus ganglion at the junction of the 6th white ramus with the 6th spinal nerve ( $G_{VIa}$ , Fig. 12). These fibers, presumably pre-ganglionic, came from the direction of the 5th level. Such displacement of ganglionic masses from their conventional positions emphasizes the anatomical distinctness of the spinal and visceral components of the sympathetic.

The 6th sympathetic ganglion lies on that division of the sympathetic-5th ramus trunk which also contains the 5th ganglion (Fig. 11). Most of its post-ganglionic fibers pass into the posterior sympathetic trunk, the other divisions of the splanchnic containing no ganglion cells. In two cases, however, a ganglion has been found on the larger of the three divisions as well (Fig. 12,  $G_{VI}$ ), whose post-ganglionic fibers passed into the splanchnic. The pre-ganglionics apparently came from the 5th white ramus. This anomalously situated ganglion then represents functionally a portion of the coeliac ganglion. Since, however, some of the fibers from the 4th level typically synapse in the 5th ganglion on their way to the splanchnic, while others synapse in the coeliac, *this extra 6th ganglionic mass bears the same relation to the 5th white ramus as the 5th ganglion does to the 4th descending ramus*. In the usual case, few fibers in this strand from the 5th white ramus synapse before they reach the coeliac ganglion. In some cases, few fibers from the anterior sympathetic trunk synapse in the 5th ganglion on their way to the splanchnic. It follows that the marked variability in the sizes of the 5th and 6th ganglia must be an anatomical variation rather than a functional one, and that those portions of the 4th, 5th, and 6th ganglia which correspond to the visceral components of the sympathetic are functionally identical with the coeliac ganglion. The coeliac ganglion can conversely be looked upon as consisting of portions of the 4th, 5th, and 6th sympathetic ganglia which have migrated distally to a position away from the sympathetic trunk, on the splanchnic nerve.

#### 7TH NERVE LEVEL

The arrangement of the 7th level is essentially like that of the 6th, a strand from the 7th ganglion to the dorsal aorta corresponding to the strand from the 6th which divides to dorsal aorta and splanchnic.

# THE COELIAC GANGLION

In some frogs no coeliac ganglion can be found, a few scattered cells occurring along the strands of a plexus around the coeliac artery. At the other extreme the ganglion consists of a large compact mass of cells on each of the three main fascicles entering from each side of the body, with smaller ganglionic masses on the finer strands of the plexus. All variations occur between these extremes. In several cases individual strands could be traced through this region along which no cells were found, while other strands had well-formed ganglionic masses. The size of the coeliac ganglion could not be correlated with the sizes of the sympathetic ganglia in the same preparation, as might have been expected if the coeliac ganglion represented parts of these other ganglia transported peripherally. Since it has been reported (Ecker and Wiedersheim, 1896) that in the greenfrog, ganglion cells and small ganglia may be scattered along the branches of the splanchnic nerve near their termination in the viscera, it may be inferred that when not present in its conventional location, the coeliac ganglion may be represented by such scattered ganglionic masses, as well as by masses of cells at the 4th, 5th, and 6th sympathetic levels, as suggested above.

When a well-formed ganglion is present, the coeliac plexus in which it is located shows a certain structural pattern related to it. The strands may anastomose and divide, but previously to entering the ganglion, a specific anastomosis occurs between the nerves from the two sides of the body. This anastomosis lies on the posterior surface of the artery, and is a pre-ganglionic one in the sense that distal to the junction of the strands from either side the common strand may contain many ganglion cells. This junction definitely involves a chiasma. From this mass a strand of fibers leaves on either side to accompany the dorsal aorta, the remainder mixes with the rest of the plexus. On the anterior surface of the artery, and distal to the ganglion, a second or post-ganglionic anastomosis occurs, from which arise several main branches of the splanchnic nerve. One or more branches arise from either side of the remaining mass whose fibers appear not to have crossed the midline. The result is effectively a ring of ganglionic tissue encircling the coeliac artery. The axis of the ring at an angle to the axis of the artery, the branches of the splanchnic leaving from the periphery of the ring along its distal margin.

## PHYSIOLOGICAL IMPLICATIONS

This histological work was undertaken in the hope of clarifying a situation reported on previously (Lucas and Miksecek, 1936; Bishop, 1937), that many fibers originating in the dorsal root ganglia of the bullfrog, but without central connections detectable in either root, produced when stimulated a massive contraction of the stomach and gut. On many of the frogs of the present series, experiments were performed similar to previous experiments on intact undegenerated preparations. The results were consistent with previous findings, and certain more specific information was obtained, although no explanation of the normal action of these fibers has been arrived at.



*Myelination.* It can be stated definitely that in the frog sympathetic many post-ganglionic fibers are myelinated, that certain grey rami to the somatic nerves are chiefly myelinated, and that their pre-ganglionic fibers are similarly myelinated. In the 5th ganglion, myelinated pre-ganglionics apparently synapse with both myelinated and non-myelinated post-ganglionics, judging by the general appearance of the fascicles in favorably distributed plexuses, without detailed fiber counts. In the coeliac and other ganglia there are certainly many pre-ganglionic non-myelinated fibers synapsing with similar post-ganglionics. In the peripheral nerves the myelinated fibers must innervate the vessels and glands of the skin, but their stimulation in the splanchnic does not cause constriction of vessels of the mesentery, nor contraction of the gut. What evidence we have points to a difference of function correlated with presence and absence of myelin, but we have not pursued the matter further. The present findings are consistent with the previous inference (Bishop and Heinbecker, 1930) that the *B* wave is that of myelinated autonomic fibers, the *C* wave that of non-myelinated fibers.

In several small strands with 3 to 300 myelinated fibers each, sections were followed through 3 mm. of nerve, and no cases were observed where myelinated fibers lost their myelin sheaths except locally at nodes. While this limited finding is not very conclusive for nerves containing thousands of fibers, it does indicate that loss of myelin is not of general enough occurrence to confuse the histological picture of degenerating nerves stained with osmic acid; nor of normal comparative counts.

*Origin of white ramus fibers.* It has appeared from previous fiber counts (Lucas and Miksecek, 1936) that a majority of the fibers of the 5th white ramus originated in the dorsal root ganglion. In our preparations after degeneration of both roots, there is so little loss in the white rami that it cannot be certainly detected, although the motor nerves show about half the myelinated fibers degenerating. This is consistent with the estimation from the fiber counts of the numbers of fibers contributed to the rami by motor root and ganglion components, respectively. Further, in favorable preparations where the degenerated motor component ran through or past the ganglion to mix with the dorsal component only well below it, the ramus bundle could be traced definitely into certain well-defined regions of the ganglion containing small cells, separate from the regions where most of the large sensory fibers had their cells of origin. The small white ramus, also, ( $W_a$ ) not only leaves the trunk before the level at which motor and sensory fibers have significantly intermingled, but it arises from the trunk on the side opposite to the motor bundle, can be traced into the region of small fibers in the ganglion, and does not degenerate after section of the roots. Since physiological experiments indicate that this fine ramus has synapses in the 5th sympathetic ganglion, it seems to contain fibers whose cells of origin are in the dorsal root ganglion but which synapse as motor fibers in outlying ganglia. In cases where the 5th ramus can be traced fairly distinctly through the splanchnic to the coeliac ganglion, large ganglionic masses appear on the fascicle representing it. The

possibility, however, that here one pre-ganglionic fiber might supply many cells of the coeliac ganglion renders the observation less critical than that concerning the smaller ramus to the 5th sympathetic ganglion.

*Root stimulation.* Stimulation of both 5th roots in the normal preparation has been reported (Bishop, 1937) to induce in the splanchnic only a small *C* wave, and no *B* wave, while stimulation of the trunk below the dorsal root ganglion produced a *C* wave 10× as high, and a pronounced *B*. We have here observed the results on gut contraction of similar stimulations. Stimulation of the roots causes slight or no contraction of the stomach and gut in our preparations; stimulation below the ganglion causes massive contraction. Contractions of the gut have been reported (Steinach and Wiener, 1895) following dorsal root stimulation in greenfrogs. We find this only if the electrodes are close to the ganglion, and the currents employed only such as to cause heating and drying of the roots at the electrodes. Such currents would presumably spread from the roots into the ganglionic mass.

That this is the explanation of presumed dorsal root activation of the gut seems more probable from the following fact. If roots of either 4th or 5th level are pulled slightly, even after crushing close to the ganglion, good contractions of the stomach and gut follow, almost comparable to those obtained by stimulating trunks below the ganglion. The effect is concluded to be from mechanical stimulation of the ganglion itself, and not of root fibers as such. Since we obtained responses from blood vessels only when the roots are undegenerated, but responses from the gut due to stimulation peripheral to the ganglion in any case, the response of blood vessels serves as a check on the intactness of the roots.

### DISCUSSION

No evidence has been obtained about how these fibers from the dorsal root ganglion, capable of activating the gut, receive stimuli in the normal body. The objection to these responses being considered as "antidromic," as various dorsal root responses have been termed, is that the fibers concerned appear not to be afferent, since they do not enter the cord. Further, the work of Tönnies (1938) on "reflex" responses over the dorsal roots raises the question whether "antidromic" is a suitable term to apply to any impulse setting up a peripheral effect. Its use here, as elsewhere, could only serve to cover our ignorance concerning the functioning of these fibers, and would suggest a similarity with the action of fibers which traverse the dorsal roots, which is premature, to say the least. We are, therefore, postponing specific conclusions concerning function until further experiments have been conducted.

### SUMMARY

In further investigation of fibers in the sympathetic nerves of the bullfrog, whose cells of origin lie in the dorsal root ganglia, but appear not to send central processes into the roots, the fiber pathways through the sympathetic system have been traced by reconstructions from serial sections and by

physiological recording of action currents. Nerve degeneration procedures were carried out on roots, rami, and trunk.

As a general pattern, with exceptions as noted, the "white" rami from a given level do not have synapses in the sympathetic ganglia of that level, but pass to ganglia at least one level above or below. There are typically two white ramus components, ascending and descending in the trunk from a given level.

The "grey" rami (post-ganglionic) of the 4th and 5th levels consist almost exclusively of myelinated fibers, with myelinated pre-ganglionics.

The splanchnic nerve is made up of rami from the 3rd to 7th levels, the 5th contributing about half the total. Some of the splanchnic fibers arise from cells in the 4th to 7th sympathetic ganglia, some in the coeliac ganglion and some are pre-ganglionic past the coeliac plexus, the positions of the synapses of these fibers being very variable. The coeliac ganglion can be looked upon, therefore, as consisting of parts of the chain ganglia which have migrated further along the fiber pathways. When, as often occurs, there are few cells in the coeliac ganglion proper, ganglia still further peripherally along sympathetic strands presumably represent the same functional elements.

A small white ramus at the 5th level can be traced into the dorsal root ganglion, does not degenerate after section of the roots, and its fibers have synapses in the 5th sympathetic ganglion. The larger white ramus at this level consists predominantly of fibers similarly originating in dorsal root ganglion cells. Most of these fibers course as far as the coeliac ganglion without synapses. Their stimulation after degeneration of the roots causes contraction of the gut, but not of mesenteric blood vessels.

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# POSTURAL NECK REFLEXES IN THE LABYRINTHECTOMIZED MONKEY AND THEIR EFFECT ON THE GRASP REFLEX\*

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## I. INTRODUCTION

THE CHARACTERISTICS of the neck reflexes vary widely among different species, especially between cats and monkeys. It has seemed desirable, therefore, to study them more fully in primate forms, and since the influence of the neck reflexes upon grasping and other prehension phenomena peculiar to primates has not previously been studied, particular attention has been devoted to these reactions. The presence of tonic neck reflexes in the thalamic monkey after bilateral labyrinthectomy was reported by Magnus (1922; see also 1924, p. 441), but his observations were limited to one animal, and the reactions were not studied in detail. For adequate analysis three principal problems must be considered: (i) In what circumstances do tonic neck reflexes appear, i.e., what projection systems is it essential to interrupt; (ii) to what extent does the labyrinth affect the neck reflexes and other reactions of the thalamic state; (iii) the characteristics of the neck reflexes themselves after the labyrinth has been destroyed. The present paper will concern itself primarily with the first and third of these problems; the second can be discussed only briefly.

## PRINCIPAL OBSERVATIONS

*Lesions essential for release of the tonic neck reflexes*

Neck reflexes can be demonstrated in the thalamic monkey (Magnus, 1922). Such preparations (labyrinth intact) exhibit a characteristic postural pattern which varies in predictable fashion when the animal's position is changed in space; thus when lying in the lateral position the undermost extremities are extended, the uppermost flexed; and the head tends to be elevated toward the horizontal position, especially during the grasp (Fig. 1);



FIG. 1. A macaque in the thalamic reflex status, but with normal labyrinths. Note that the head tends to be held off the table and that grasping is present only in the uppermost extremity.

when turned over the entire pattern reverses. For convenience these stereotyped attitudes have been referred to as "the thalamic reflex pattern." The pattern appears when certain specific cortical projection systems are interrupted. Thus Bieber and Fulton (1933, 1938) observed it in macaques from which areas 6a (upper part) and 4ab of the Vogts had been removed bilaterally (Fig. 2). In such preparations they also found that the grasp reflex formed a part of the postural pattern, being more strongly present in the uppermost limbs and weaker, or absent, in the under limbs when the animal lay on its side (Fig. 1). They inferred from this and other evidence that the grasp reflex is a part of a generalized postural reflex pattern which can be influenced by the labyrinthine, the body righting, and presumably also the neck reflexes. Bieber and Fulton (1933, 1938), however, were able to demonstrate tonic neck reflexes consistently in only one of their bilateral area 4-and-6 preparations; they therefore concluded that some projection systems other



to indicate an extensive *bilateral* interruption of the motor projection systems from the frontal lobes. It is not yet clear whether the projections from area 9 of the prefrontal regions influence the thalamic reflex pattern or the neck reflexes. From the evidence just outlined, one may infer that the influence of these projections is not great in the adult animal.

### *General effects of labyrinthine destruction*

FFA monkey having areas 4 and 6 completely removed, exhibiting the thalamic pattern, differs in three important respects from such a preparation lacking its two labyrinths. The latter has: (i) absence of head righting reflexes (Fig. 3); (ii) generalized diminution of postural contraction (cf. Figs. 1 and 3); (iii) absence of post-rotatory and caloric nystagmus. Our comparisons are based on animals which were first labyrinthectomized. (We have not yet had



FIG 3 A labyrinthectomized macaque in the thalamic reflex status following simultaneous bilateral ablation of all of areas 4 and 6, except area 6b $\beta$  (see Fig. 2) Note that there is no tendency toward head righting and that the thalamus pattern, though present, is not intense.

opportunity to destroy the labyrinth of an animal from which areas 4 and 6 had been removed as a primary procedure.) The differences between the two animals are conspicuous and may be summarized as follows:

*Absence of head righting reflexes.* When a bilateral 4-and-6 preparation with normal labyrinths is placed in the lateral position the head may often be held off the table and tend to assume the horizontal position (Fig. 1; see also Fig. 3 of Bieber and Fulton, 1938). When the animal is held upright, the head assumes an upright position as a matter of course; indeed, when the animal is suspended, the tendency toward head righting is clearly apparent. In bilateral 4-and-6 preparations without labyrinths, the head seldom assumes the horizontal position; indeed it wobbles around into any position into which gravity may draw it, and when the animal is placed on its side, the head is not ordinarily raised from the table (Fig. 3).

*Generalized diminution of postural resistance.* The thalamic reflex pattern is conspicuously present in the bilateral 4-and-6 preparations without labyrinths, and it conforms in all respects with that found in such a monkey with intact labyrinths, except for slight weakness of the grasp reflex and for generalized diminution of postural resistance. Particularly conspicuous is the diminished resistance to passive manipulation of neck muscles, and the corresponding flaccidity of the semi-flexed uppermost limbs when the animal is in the lateral position. *The labyrinth thus appears to give greater intensity to all attitudes of the thalamic reflex pattern* (contrast Figs. 1 and 3), but it is clearly not responsible for the basic pattern itself.

Removal of the labyrinths facilitates the analysis of the thalamic reflex pattern, since turning the animal over or moving through space does not precipitate a "barrage" of labyrinthine righting reactions. In keeping with Magnus' analysis (1922), the sensory origin of the pattern can be traced to asymmetrical stimulation of the trunk and lateral surfaces of the thigh; they thus fall into the category of body righting reflexes acting on the body. With the animal on its side application of uniform pressure to the uppermost surface of the body ("board test") causes the posture of the limbs to become symmetrical, and inhibits the grasp reflex of the uppermost extremities. Pressure on the thigh alone, and especially on the trochanter, equalizes the hind limbs and diminishes the grasp and the asymmetry of the fore limbs.

*Rotatory nystagmus.* Following bilateral labyrinthectomy in the otherwise intact animal, post-rotatory and caloric nystagmus cannot be demonstrated. If the animal is observed when its eyes are closed or when they are covered by a 20-diopter lens, there is no nystagmus during rotation. If free to fix on objects outside the rotating table, however, a visual or "railroad" nystagmus is seen during rotation. Although this was present in every case prior to the ablation of areas 4 and 6, it was never observed in these animals following ablation of these cortical areas. Post-rotatory nystagmus and caloric nystagmus occur regularly in animals with bilateral ablations of areas 4 and 6, when their labyrinths remain intact.

#### *Neck reflexes and the grasp reflex*

The tonic neck reflexes of a macaque with areas 4 and 6 removed bilaterally are similar to those observed in decorticate human beings.\* When the jaw is rotated toward the right the right limbs become extended and the left limbs flexed. Exactly the same pattern of response is seen in such preparations when the labyrinths had been previously removed, but all postures assumed are less intense in the labyrinthectomized animals. In these respects the tonic neck reflexes are similar to those described by Magnus (1924) in lower vertebrates. The conspicuous changes in the grasp reflex which occur in association with the neck reflexes have not previously been described.

\* It has been pointed out elsewhere (Fulton, 1938) that the majority of reports of human beings exhibiting tonic neck reflexes indicate that the cases in question showed signs, not of decerebrate, but of decorticate rigidity.



The grasp reflex changes in intensity with the animal's position in space, being well developed in the flexed uppermost extremities when the animal



FIG. 4. A. The same animal as in Fig. 3 showing neck reflexes on rotation of the head to the right. B. The same a few seconds later with head rotated to the left.

lies in the lateral position and absent in the undermost extremities (see above). Studies of the neck reflexes indicate that the *grasp reflex* is invariably seen in

those extremities which, through operation of the tonic neck reflexes or of the body righting reflexes, assume a flexed posture. Thus, on rotation of the head (a) the "jaw" limbs show: (i) an extended posture; (ii) increase in resistance to passive flexion, and (iii) diminished or absent grasp reflex in both upper and lower extremities; (b) the "skull" limbs show: (i) a flexed posture, (ii) diminished resistance to passive flexion and (iii) conspicuous increase in the grasp reflex of upper and lower extremities. As indicated in Fig. 4A and B these effects are reversed by changing the direction of head rotation. The changes occur after a latency of 1 to 2 secs.

On extension of the neck all extremities show: (i) an increase in extensor posture, (ii) increased resistance to passive flexion and (iii) diminution of the grasp. On flexion of the neck: (i) all four extremities tend to assume a flexed posture, (ii) resistance to passive flexion is decreased, and (iii) there is marked increase in the grasp reflex, especially of the upper extremities. Other manoeuvres such as rotation of the pelvis produce changes of a similar nature in the hind limbs, i.e., the flexed limb shows the grasp reflex, and the extended limb a diminished or absent grasp.

### DISCUSSION

The grasp reflex is released through bilateral removal of areas 4ab and 6a (upper part), but the reaction does not become influenced by the neck muscles until the neck centers are themselves released through bilateral ablation of face areas 6a (lower part) and 4c. In these circumstances the grasp becomes conspicuously influenced by neck rotation, as are the other attitudinal reactions of Magnus. The fact that enhancement of the grasp is invariably associated with an increase in flexor posture is also significant, indicating that grasping is not an isolated reaction, as some have inferred, but rather an integral part of the flexion pattern of postural response in primate forms. As such it is influenced by the neck muscles and no doubt also by the labyrinth. The exact character of the labyrinth's influence on the grasp remains for future analysis, but it clearly takes part in the righting reflex patterns originating in the labyrinth.

### SUMMARY

The thalamic reflex status appears in adult monkeys following isolated removal of areas 4 and 6 of Brodmann from both cerebral hemispheres. Tonic neck reflexes can also be demonstrated in such preparations, provided the motor and premotor face areas (areas 4c, 6a, lower part of the Vogts) have been completely removed from both sides in addition to areas 4ab and 6a (upper part). The thalamic reflex status has been thus induced in 5 previously labyrinthectomized monkeys and one baboon and the tonic neck reflexes studied in detail. The general reactions are similar to those described by Magnus and de Kleyn for cats and dogs, but the primate shows, in addition, conspicuous changes of intensity of the grasp reflex. When the animal lies supine and the chin is rotated well to the right side, the right extremities become extended and the grasp reflex is absent; the left extremities become flexed and the grasp reflex

is well marked. Furthermore, any postural reaction, whether originating from neck or body, that produces increase of a flexor posture in an extremity also causes *intensification of the grasp reflex*; any postural reaction causing increase in extensor posture causes diminution of the grasp reflex. The grasp reflex in primate forms thus becomes a part of the postural reflex mechanism.

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# THE INFLUENCE OF POSTURE ON RESPONSES ELICITABLE FROM THE CORTEX CEREBRI OF CATS

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## INTRODUCTION

CLARK AND WARD (1937) described a unipolar electrode by means of which the same point on the cortex cerebri of unanesthetized and unrestrained cats can be stimulated at will over a period of several weeks or more. Using these electrodes they found that like movements could be elicited from a fixed point on the cat's motor cortex from day to day. Occasional variations in these movements were observed, however, when the animal was stimulated after it had altered its posture. These variations occurred after the variables described by Graham Brown and Sherrington (1912), (facilitation, inhibition and strength of stimulating current) were controlled. The present experiments were undertaken to determine the extent of the influence of different postures on movements elicited by stimulation of the motor cortex by anesthetized cats. The results demonstrate that in an analysis of the mechanisms involved in the production of responses from the motor cortex by electrical excitation the position of the head at the moment of stimulation and also the position of the leg responding to the stimulus are of paramount importance. Emanating from these observations is the idea that stimulation of the motor cortex does not necessarily produce specific movements, but rather that it causes the leg responding to the stimulus to assume a position specific for the cortical point excited.

## MATERIALS AND METHODS

Permanent electrodes were placed on the anterior sigmoid gyrus of 22 cats, using the method described by Clark and Ward (1937). The fixed cortical points were stimulated at intervals over a period of several weeks with a weak, 60-cycle sine wave current. The current was taken from the 110 volt lighting circuit and passed through a transformer (Myers, 1936) from which fractional voltages from 0 to 16 could be obtained. For each stimulus a record was kept of the following points: (i) the strength of the stimulating current, (ii) the response in terms of movement, (iii) the latency of the response (the interval of constant stimulation at a fixed voltage before the appearance of the primary movement), (iv) the general posture of the animal, (v) the initial position of the particular extremity in which the primary movement occurred, and (vi) the animal's emotional state at the moment of application of the stimulus.

Kymographic records were made of the responses in some instances. The extremity affected by the cortical stimulus was attached to a heart lever with a thread. The lever was supported by a light spring and directly recorded flexor or extensor movement. One signal magnet marked the time in seconds; another the moment of application and the duration of the stimulus. In order to control proprioception, the extremity responding to the cortical stimulus was deafferented in two animals and in two others the sensory fibers of the first four cervical nerves were cut bilaterally. These animals were studied during the two weeks that they were allowed to survive.

\* National Research Council Fellow, 1936-1937.

The electrodes used were slightly different from those previously described (Clark and Ward, 1937). Cortical injury was reduced to a minimum by having the electrodes pressed firmly against the pia-arachnoid, causing only a slight indentation rather than breaking through. The stigmatic electrode was constructed of a platinum wire fused into a small glass tube with its end rounded in a flame and the wire filed flush with the rounded surface of the glass. The other end of the platinum wire was enlarged with a drop of solder for contact with the stimulating leads. The wire-containing glass tube was then fitted tightly into the threaded end of the stainless steel tube by means of a short segment of rubber tubing. Only the rounded part of the glass (about 1 millimeter) protruded from the threaded end of the steel tube. The remaining construction of the electrode and that of the contact plug with its leads from the stimulating apparatus was similar to that previously used.

## RESULTS

Rhythmic and non-rhythmic movements elicited from specific cortical points were studied in the various cats. In general, rhythmic movements may be divided into two parts; the first part is not rhythmic and moves the responding leg (the extremity affected by the cortical stimulus) into a position from which the second part of the movement, the rhythm, occurs. "Batting" and "digging" are examples of such movements elicitable from the motor cortex of cats. In a given animal, with currents of proper strength, the rhythm of these movements develops each time only after the responding leg has been moved by the non-rhythmic portion of the movement (or by hand) into approximately the same position. Ordinarily this position for "batting" is one of partial protraction of the shoulder, partial extension at the elbow and supination of the paw. This position will be called the "final position" for the sake of convenience and for other reasons to be brought out later. In other animals the stimulation of their respective cortical points often evoked simple movements such as flexion or extension with no rhythm. For these movements, also, a "final position" was elicited if the stimulus were of the proper length and strength. The final position for such movements usually appeared to be at the maximal extent of movability of the responding leg in the direction of the movement, *i.e.*, maximal extension or maximal flexion, but this was not always the case. Repeated experiments indicated that under similar conditions of posture and strength of stimulus, the final position for a given cortical point exciting a rhythmic or a non-rhythmic movement was always the same. Stated in another way, the response elicited from a single cortical point was always similar when the same conditions of posture and technic of stimulation obtained for each stimulus.

### *Variations of the elicited movements induced by altering the position of the responding leg*

Figs. 1 and 2 illustrate the variations obtained by stimulating points that produced non-rhythmic and rhythmic movements, respectively, when the position of the responding leg was altered between stimuli. In each instance the stimulus was stopped as soon as the character of the movement was ascertained. In cat 24 (Fig. 1) the response was a movement carrying the right foreleg into a final position of extension with some shoulder protraction.

In this instance the cat was lying on its left side while the left cortex was stimulated at one-minute intervals with a current of fixed strength (2.65 volts). In the first tracing at the number 1, the responding leg was relaxed in a flexed position against the body before the stimulus was applied. The stimulus caused the leg to be partially extended, indicated by the upward direction of the response line. The leg was allowed to remain in the position taken as a result of the stimulus (partially extended) and a repetition of the stimulus (number 2) caused the leg to be further extended. After another minute a third stimulus (number 3) caused the leg again to be extended from the second induced position into maximal extension.

By three successive stimuli the leg was moved into the final position. Longer stimulation caused no further movement until a convulsive effect was induced (Ward and Clark, 1938). A single continuous stimulus of about 3 sec. duration in this animal caused the leg to move from full flexion into the final position of maximal extension.

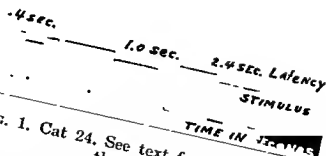


FIG. 1. Cat 24. See text for description of the figure.

In cat 31 (Fig. 2) rhythmic battling occurred if the stimulus of proper strength was applied long enough. Using only the first part or non-rhythmic portion of the movement it was possible to obtain complete reversals of the response at successive stimuli by placing the responding leg in a flexed position before a stimulus of constant strength (2 volts) was used in each instance. The cat was lying quietly on its left side and a point on the left motor cortex was stimulated. In the first response the responding leg was passively flexed against the body prior to the stimulus. As a result of the stimulus the leg was moved into a partially extended and protracted position; this is indicated by the downward direction of the curve in the first tracing. One minute later the stimulus was applied again after the cat's leg had been placed in an extended position where the cat allowed it to remain quietly. The stimulus (second tracing) caused the responding leg to be flexed, a complete reversal of the previous effect. The third response was obtained one minute later after the leg had been flexed but

this time less than it had been for the first response. The response was like that obtained with the first stimulus, *i.e.*, downward, indicating extension and protraction, toward the final position. These results could be repeated a number of times without fatiguing the cortical point stimulated if one-minute intervals were maintained between stimuli. Similar results are illustrated in Table I in which a larger number of responses are included.

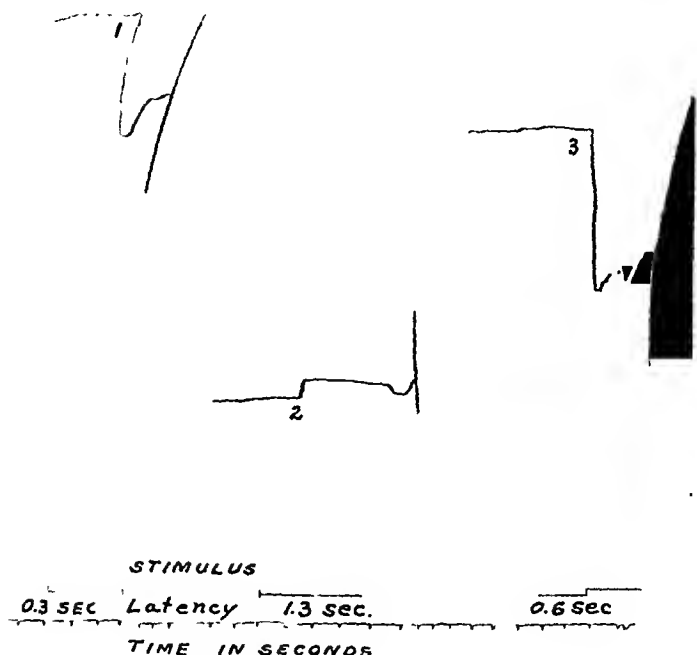


FIG. 2. Cat 31. See text for description of the figure.

From these three examples it is evident that various muscles can be brought into play at different times as a result of stimulation of a single cortical point merely by altering the position of the responding leg prior to the application of the stimulus, and it appears that the stimulation of a cortical point elicits movements that convey the responding leg into a position specific for the point stimulated, *i.e.*, the final position.

*Latency variation initiated by altering the position of the responding leg in relation to the final position*

The variations in latency (the time between the beginning of the stimulus and the onset of movement) that occur with responses elicited by currents of fixed strength from a single cortical point are great if the stimulus is of the proper intensity. Invariably an alteration of the length of the latency accompanies an alteration in the initial position (the position of the leg when the

stimulus is applied) of the responding leg. This is illustrated in the following examples for both rhythmic and non-rhythmic movements. In cat 24 (Fig. 1) the movement elicited was simple extension and the final position was near or at maximal extension of the responding leg. For the first stimulus when the leg was placed farthest from this position, *i.e.*, flexed against the body, the latency calculated from the coordinates in the figure, was short (0.4 seconds). With the leg in an intermediate position between flexion and extension for the second stimulus, the latency was longer (1.0 seconds), and for the third response with the leg almost fully extended and approximating the final position, the latency of the response was found to be longest (2.4 seconds).

Table 1

Stimulus	Position of Responding Leg When Stimulus Was Applied	Response	Latency
1	Partially flexed	Extension	4 3 sec
2	Protracted and extended	Slight flexion (with-drawal)	8 4 sec
3	Protracted and extended	Slight flexion	8 0 sec
4	Flexed	Extension	4 0 sec
5	Retracted and flexed	Protraction and Extension	3 9 sec
6	Flexed, less than in No 1	Protraction and Extension	6 4 sec
7	Strong extension	Flexion	4 9 sec
8	In final position	Rhythmic batting, slow, began with adduction and supination of paw	10 4 sec.
9	Flexed against body	Extension	2 8 sec

Cat 36 Rhythmic batting was elicitable in this animal with a long stimulus of 2.5 volts. In most instances, however, the current was applied only long enough to induce a partial response. The cat was lying on its left side and the left motor cortex was stimulated through a permanent electrode. A stop watch was used to measure the interval between the application of the stimulus and the appearance of the movement, *i.e.*, the visible latency of the response.

As pointed out above, the final position for rhythmic batting is often somewhere between full extension and full flexion, and the length of the latency is dependent again on the position of the leg when the stimulus is applied relative to the final position initiated by the stimulus, regardless of whether the starting position of the leg is on one side or the other of the final position. Thus, in the first response of Fig. 2 (cat 31; the movement, rhythmic batting) the leg, when the stimulus was applied, was farther from the final position than in either of the other two responses, and the calculated latency of the extension that occurred was the shortest of the three (0.3 seconds). For the second response the leg was extended slightly beyond the final position and flexion occurred with the stimulus after a long latency (1.3 seconds). For the third response the responding leg was flexed and a distance



from the final position intermediate to the other tests. The latency of the extension that occurred was also intermediate (0.65 seconds). A similar relationship is shown by the latencies of each of the responses listed in Table 1. The starting positions were irregularly altered and the results demonstrate that fatigue is not a factor in the changes in the latencies at successive stimuli delivered at one-minute intervals. It is obvious from these and similar experi-

Table 2

Table 2

Stimulus Number	Strength of Stimulus (volts)	Latencies		
		Head right	Head center	Head left
1	1.5	8	8 7	4
2	1.5			
3	1.5			
4	1.1	8	8 7	6
5	1.1			
6	1.1			
7	1.1	6	8 7	5
8	1.1			
9	1.1			
10	1.1	7	8 7	4
11	1.1			
12	1.1			
Results below obtained the following day; conditions same as above.				
1	1.3	No response*		4½
2	1.3			
3	1.3			
4	1.3	No response*		4
5	1.3			
6	1.3			
		No response*		5

\* Stimulus applied about 10 seconds.

Cat 24. The right motor cortex was stimulated at approximately one-minute intervals, and after each response the responding left foreleg was replaced as nearly as possible in the original position. The response was a simple extension and protraction. The cat's attention was attracted to one side or the other or to the front as indicated in the table. While the head was in a given position, the stimulus was applied and the moment at which movement was noted in the responding leg was recorded. The figures in the three right hand columns are the latencies in seconds of the various responses. In the last series it is noted that with the stimulus used no response was visible when the cat's head was turned away from the responding leg while it appeared consistently when the head was turned toward it.

ments that the length of the latency of a response is related to the distance of the initial position of the responding leg from the elicitable final position decreasing as the leg is placed further (in any direction) from the observed final position.

#### *Effect of variation of position of the head on the final position*

That the position of the head of the animal affects the final position elicited is evident from the following experiments. When the head of cat 24 was turned to the right as it lay in a hammock or prone on the table at the

moment of application of the stimulus, the stimulus caused the responding right foreleg to be extended and to abduct. With the head turned to the left the next stimulus caused extension accompanied now by adduction. The extension elicited with the head in the midline was not associated with either abduction or adduction. Care was taken to see that the shoulders did not shift with changes in position of the head. Rhythmic movements, such as batting, could be affected similarly by changing the position of the head. The batting movements were thus directed to either side or to the front by appropriately turning the head to one side or the other or by allowing it to remain forward.

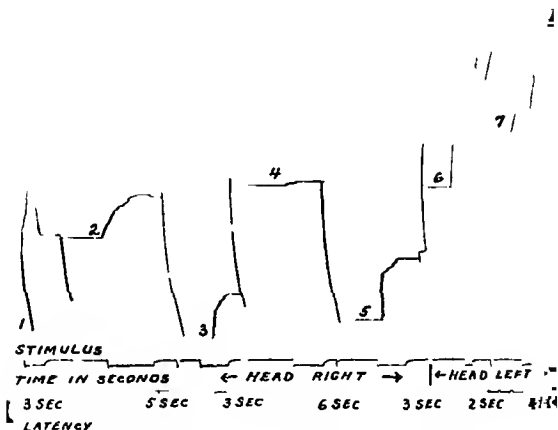


FIG 3 Cat 25 See text for description of the figure

when the stimulus was applied. Further, raising the head during the stimulus led the responding foreleg to flex more at the elbow so that the batting took place on a higher plane than before. Lowering the head similarly caused batting in a position more nearly under the animal. These observations make it appear that the leg final position elicited from a fixed cortical point shifts with the head position so that it follows the nose of the animal. Similar results were obtained with the animals blindfolded.

*Effect of the position of the head upon the latencies  
of the responses*

During experiments conducted on cat 24 while it was lying sphinx-like, there were variations in the latency of the responses of the foreleg which

appeared to be related to the position of the cat's head during stimulation. Examples of such results are recorded in Table 2. They indicate that the

latency is shortest when the head of the animal is turned (lateral flexion) toward the responding leg and lengthened when the head is turned away from it. Kymographic records of the responses elicited from cat 25 (Fig. 3) show a similar relationship. A point on the right cortex was stimulated with currents of fixed strength (4.25 volts) at one-minute intervals. The response, extension in the left foreleg, is indicated by an upward movement in the figure. The first five responses were obtained with the head turned towards the right and show longer, calculated latencies than do the later ones. This occurred even though in the later tests the initial leg position was closer to the final one, so favoring a longer latency.

A number of responses, about 10 each in one experiment, were obtained with the animal's head turned to either side and the latencies averaged for each position. These records also showed that the latency when the head is turned away from the responding leg is about 10 per cent longer than when turned toward it. Such observations were not obtainable in all animals studied.

The length of the latency was also altered characteristically by holding the head in a raised or lowered position. As is shown in Fig. 4, the latency is shorter when the neck is extended and longer when it is flexed forward. The animals were quiet in these and other similar experiments.

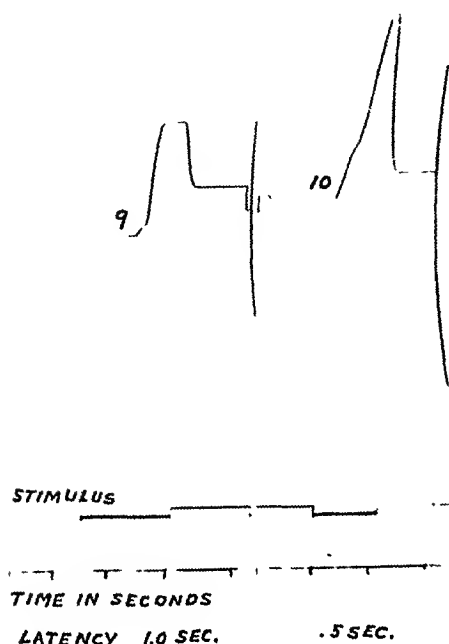


FIG. 4. Cat 25. The animal was lying prone in a body cast with its legs freely movable. It had received 10 milligrams of nembutal two and one half hours prior to the experiment (in other experiments it has been observed that approximately 15 milligrams per kilogram of body weight will cause a loss of the placing reactions in the cat for only thirty to forty minutes). The right motor cortex was stimulated with currents of fixed strength (1.75 volts) at one-minute intervals. For the first response (marked with a number 9) the cat's head was down and in the midline. The response was simple extension of the leg occurring after a calculated latency of 1 second. The cat's head was then raised so that the nose-occiput angle was  $45^\circ$  above the horizontal and held there for the second stimulus. This response (marked with the number 10) contained in it some protraction with the extension, and the calculated latency was 0.5 seconds.

*Effect of deafferentation of the responding leg on  
latency of responses*

In two animals the lower five cervical and the first two thoracic dorsal roots on the right were sectioned extradurally. The general pattern of the responses elicited in the deafferented leg of each animal during several weeks after its operation was similar to that obtained before, but the movements were jerky and poorly coördinated. Rhythmic batting was elicited in one of the animals. Other than the jerkiness of the movements, the only effect of the dorsal root section was to make remarkably constant the latency of the response for a given strength of stimulus regardless of the initial position of the responding leg. Increasing the strength of stimulus shortened the latency.

*Effect of bilateral section of the first four dorsal roots on  
the final position and on latency*

Because the final position elicited from a given cortical point appeared to shift so as to follow the nose with changes in the position of the head, the first four cervical sensory roots were sectioned on both sides (motor and sensory components of the first and the second nerves were cut outside of the vertebral canal at their exit from the latter, and the dorsal roots of the third and fourth cervical nerves were sectioned extradurally). In two animals tested during two weeks after operation, turning the head to either side or flexing or extending it did not produce the normal shift in the elicited final position, and latencies with currents of fixed strength were independent of head position. These findings were repeated frequently in the two operated animals during the two weeks of their survival.

*Effect of environment on the latency of the responses*

Bubnoff and Heidenhain (1881) have shown in dogs anesthetized with morphine that the latency of a response elicited electrically from the motor cortex is shortened by a few hundredths of a second as a result of coincident cutaneous nerve stimulation. Variations of remarkably greater magnitude were observed in the present experiments on unanesthetized cats as a result of normal cutaneous impulses or by auditory stimuli given just prior to the cortical ones. Figure 5 illustrates this in cat 37, a normal animal. The cat was lying on its left side, and the left cortex stimulated at one-minute intervals with a current of fixed strength (2.5 volts). The response in the right foreleg was retraction at the shoulder and flexion at the elbow. The letters under the responses indicate the following: *R*, the animal was undisturbed for about 1 minute; *P*, the cat was rubbed briskly 10 seconds before the application of the stimulus; and *S*, a sharp sound was made a few seconds before the application of the stimulus. Similar results to those shown in the figure could be obtained repeatedly with stimulation of the cortex. It is evident from the variations in latency demonstrated in the figure, that unusual noise or handling of the animal may reduce their length by almost one half. The state induced by these procedures lasts for a variable interval from a few

seconds to minutes depending on the disposition of the animal. In the cited experiments, the original latencies were obtained after a one-minute respite. Such vacillation of the latency under the influence of various environmental conditions may be of considerable importance in determining a threshold for cortical points in the unanesthetized or lightly anesthetized animal.

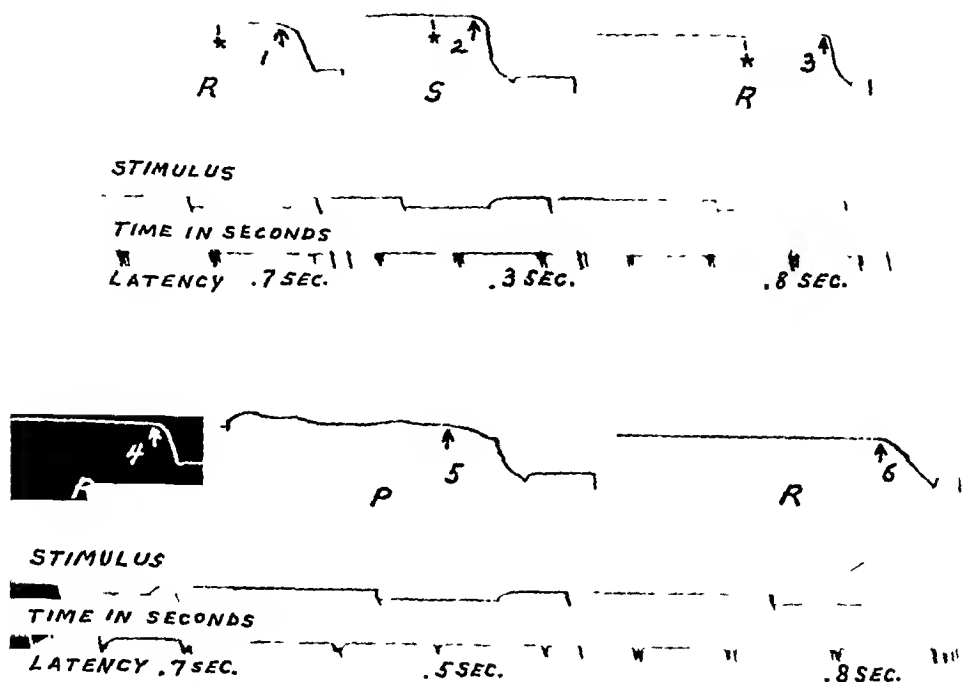


FIG. 5. Cat 37. See text for description of the figure. In the first three responses the stars indicate the moment of application of the stimulus, and the arrows indicate the beginning of the response.

### DISCUSSION

The question of the stability of a motor cortical point in relation to the movement elicited from it by electrical stimulation has been of great interest not only in the study of cortical physiology but also in the study of pathological states which involve the cortex and deal with cortical localization of function. It has been shown (Clark and Ward, 1937, p. 16) "that the same response can be elicited from the same cortical point from day to day, and (the experiments) argue against any marked instability of cortical points except under the temporal influence of transient physiological states." This generalization is borne out by the present experiments, which demonstrate some of the fundamental factors responsible for alterations in the movements elicited by electrical stimulation of fixed cortical points in unanesthetized animals.

It appears that neither specific muscles nor specific movements are necessarily represented under specific points on the motor cortex, although the same movements can be elicited repeatedly at will by stimulation of a cortical point if the posture of the animal is unaltered. Rather, electrical excitation of a cortical point causes the responding leg to assume a more or less constant position. This position has been called the final position, and the movements that occur in attaining it may be many and varied, depending on the position of the responding leg prior to the application of the stimulus. Further evidence that such a point specificity exists in the cortex is found in the observations that the length of the latency of the responses varies inversely to the distance of the initial position from the final one.

The explanation for the constancy of latency (with fixed stimuli) after deafferentation of the responding leg is not clear. It is evident, however, that the variation in latency associated with initial position of the responding leg is dependent upon the proprioceptive afferents of that leg. This suggests that tone is an important factor in controlling latency; especially since Sherrington (1921) has shown that tone is fundamentally associated with a proprioceptive reflex. As further evidence, the animal's general state of excitement (general bodily tone) often determines the length of latency, and also increased activity of tonic neck reflexes tends to shorten the latency, other factors being constant.

The effect of the tonic neck reflexes was first demonstrated on a background of extensor hypertonus in the decerebrate animal by Magnus and de Kleijn (1912) and later (1915) in certain pathological conditions in man. Lissitza and Pentzik (1934) have studied the effect of the tonic neck reflexes on the contralateral legs of conscious dogs for a few days after removal of cortical area 4 on one side. Hines (1937) has observed the influence of these reflexes on the posture of the legs in a monkey as long as 20 months after the bilateral removal of areas 4 and 6, exclusive of the face areas. In the present experiments changes in the position of the head have been shown to cause a shift in the final position, which seems to follow the nose of the animal. Most of the change occurs at the shoulder girdle. This dependence of final position on head position is lost if the sensory fibers of the first four cervical nerves are cut bilaterally, thus again demonstrating the importance of the neck reflexes. Somewhat similar changes in the position of the leg in rhythmic activity are caused by slight shifts in the position of the stimulating electrode in acute experiments on anesthetized cats (Ward and Clark, 1935). An altered electrode position, however, cannot explain these results in the conscious animal since the shift in final position is lost after deafferentation of the upper cervical region. This relationship between the head position (acting through the sensory fibers of the upper cervical nerves) and the final position of the leg demonstrates how postural reflex activity may cooperate with cortically initiated activity to insure coordinated responses with the least effort on the part of the higher centers.

The differences in latencies of individual responses, which result from

altered head position, were often variable and small. Nevertheless, the interpretation that they are the result of tonic neck reflexes acting on the responding leg is strengthened by the fact that deafferentation of the neck muscles (supplied by the first four cervical nerves) obliterates them. The variability in the results might be explained on the basis of an altered state of excitability of the animal at the moment of stimulation; because, as has been shown, the level of excitement has a marked influence on latencies for successive stimuli at a given cortical point. Sherrington (1920, p. 232) has said that, "The tonic reflexes of attitude are of habitually low intensity, easily interfered with and temporarily suppressed by intercurrent reflexes, these latter having higher intensity." Even though the "reflexes of attitude" persisted in such a field, their intensity is so low that their comparative influence from stimulus to stimulus could easily be masked by the more potent effect of this rapidly changing general excitatory (emotional) state of the animal.

The question of a possible effect of the labyrinths on the latency of responses and on changes in the final position with altered head positions naturally arises. No experiments were done directly to test their effect. The observations on the influence of head position were made when the head was stationary; and, except when the head was in a raised or a lowered position, the nose-occiput angle with the horizontal was approximately the same in each instance. Figure 4 may find part of its explanation in the effect of the labyrinthine mechanism because Magnus (1924) has shown that a greater increase in tone is occasioned in the forelegs by this mechanism when the head is back ("plus 135°") than when it is bent forward ("minus 135°"). Since changes in the position of the head produced no effect on the final position or on the latencies after deafferentation of the upper cervical region, it seems likely that the labyrinthine mechanisms do not play an important part in these processes, at least under such conditions.

Numerous methods have been employed to determine how skeletal muscles coöperate to produce smooth and effective motion. These have been presented in complete form by Tilney and Pike (1925) who discuss the relative merits and demerits of the various procedures. Using the method employed by the Sherrington School, in which the leg was fixed and strings were fastened to the detached tendons of antagonistic muscles so that their movements were recorded simultaneously, they observed irregular variations in the simultaneous activity of the antagonistic muscles of the leg, induced by electrical stimulation of the motor cortex. It appears likely that this variability was due to altered proprioceptive impulses coming from the antagonistic muscles whose tendons had been cut; for with a given initial posture of the responding leg (normally innervated) and a known final position elicitable from a particular cortical point, we can predict for each stimulation the resultant contractions of groups of muscles in terms of movement and even the relative latency of the responses.

## SUMMARY AND CONCLUSIONS

1. Under fixed conditions of posture, localization of function in the motor cortex appears to be constant in that a specific "final position" is elicited in the leg affected by the stimulus

2. By altering the position of the responding extremity over a wide range, before each stimulus to a fixed cortical point, the movement elicited may be altered and even reversed, but the same final position will be attained each time (other postural factors constant)

3. Differences in latency of responses for different initial positions of the responding part support the conception of a final position.

4. The final position is modified by certain postural reflexes.

5. The latency of responses is markedly influenced by the general emotional state of the animal at the moment of stimulation; thus a variability of the "threshold" of cortical points can occur even with currents of fixed strength and for fixed postures

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# REORGANIZATION OF MOTOR FUNCTION IN THE CEREBRAL CORTEX OF MONKEYS DEPRIVED OF MOTOR AND PREMOTOR AREAS IN INFANCY\*

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## INTRODUCTION

ABLATION of the motor and premotor regions (areas 4 and 6 of Brodmann; Fig. 1) from the cerebral cortex of the *adult* monkey profoundly affects motor

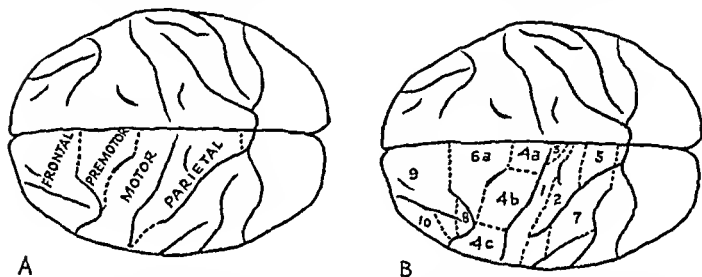


FIG. 1. A. Diagram of cerebral cortex of *Macaca mulatta* showing approximate boundaries of the areas extirpated; the "motor" regions, *i.e.*, motor and premotor areas; and the regions not primarily concerned with motor function, *i.e.*, the frontal and parietal areas.

B. Map of the cerebral cortex of *Macaca mulatta*. (Modification of Brodmann's

In a previous series of experiments<sup>6</sup> it was shown that in the *adult* monkey after any cortical lesion a number of factors affect the rate and extent of motor recovery. Bilateral ablation of areas 4 and 6 deprives an adult of virtually all "volitional" movement; yet, if one part of either area remains, some purposeful movements are regained. So, although discrete parts of the motor area are known to integrate isolated movements of face, arm or foot, each part of the motor area appears, in addition, to be capable of mediating reactions in other extremities.

There is evidence in addition that cortical fields other than areas 4 and 6 play a part in elaborating motor activity; thus primary removal of the frontal association areas, or of the parietal lobe, has little effect on motor performance; *yet if one or more of these regions is removed in conjunction with areas 4 and 6*, the resultant disability is greater and lasts longer than in animals in which areas 4 and 6 alone are destroyed.<sup>6</sup> The slight recovery appearing after bilateral ablation of areas 4 and 6 may owe its existence to these regions. The duration of the interval between successive ablations also directly affects ultimate motor capability. When the interval is long enough to allow the maximum recovery, a second operation is followed by less deficit; when performed earlier, paresis is greater.<sup>6</sup>

In the *infant* monkey all the factors which affect recovery in the adult also obtain; but in infants, the extent of recovery after any given cortical ablation is always much greater than in the adult. The present paper is concerned with a study of this restitution of function and with the identification of the regions, either cortical or subcortical, responsible for mediating the highly skilled acts which develop in infant monkeys in the complete absence of the classical motor cortex.

#### TERMINOLOGY AND METHOD

For purposes of exposition the cerebral cortex may be divided into two parts: (i) the areas of accepted motor function and (ii) the remainder of the neopallium in which motor activities are ordinarily overshadowed by other functions. (Fig. 1.) The "motor" regions consist of the motor and premotor areas (*i.e.*, areas 4 abc and 6 ab upper part of the Vogt's modification of Brodmann's map, Fig. 1B), which, in the adult monkey, are essential for purposeful movements. The regions of less conspicuous motor function are: (i) the frontal association areas (areas 8-12 of Brodmann) *i.e.*, all cortical tissue in the frontal lobe rostral to the "motor" areas; (ii) the postcentral gyrus (areas 3-1-2) and part of the posterior parietal lobule (area 5 of Brodmann). It is recognized that area 8, the motor region for conjugate eye deviation, is also a motor area, but for various reasons it has been placed in the second category, since its effect on the motor performance of the extremities with which this paper is chiefly concerned is insignificant.

Observations have been made on 15 infant monkeys, 12 rhesus (*Macaca mulatta*) and 3 baboons (*Papio papio*) born in Laboratory. The procedure consisted in removing portions of cortical tissue from one hemisphere under ether anesthesia, during the fourth week of life. The infants were then allowed to develop without further operation until the sixth month, or thereafter, when cortical regions were removed from the second hemisphere. Detailed records (written and photographic) were kept of motor performance, behavior and development; abstracts from representative histories are recorded in the protocols below. Histological studies are being made of the tissue removed at operation, and from the brains after autopsy. These will be reported in detail later when the studies of the animals now living have been completed.

## EXPERIMENTAL DATA

The normal infant macaque has a relatively high degree of independent motor function at birth as compared with man and anthropoid. All new born monkeys cling unaided to their mothers and suck at the nipple a few minutes after birth; they continue to exhibit these behavior patterns for the first few weeks of life. Although there is considerable variation in motor ability—which generally appears to correlate with the weight and size of the infant at birth—all new born infants placed on a flat surface will promptly right themselves and a few are able to stand somewhat unsteadily and on a broad base. By the second week they can stand and crawl, but still with tremulous uncertainty and they begin to bite at solid food. During the third week progression is more accurate but the grasp reflex and the tendency to cling is still dominant. Shortly thereafter, during the fourth or fifth week, purposeful use of the hands begins. At this age, voluntary release of grip appears, the infants leave the mother, and move about exploring objects and touching them with the face or hands. They do not begin to feed or use the hands or to pick up objects until the middle or end of the second month. In this series, therefore, lesions made during the fourth week of life occurred at a time when voluntary movement was minimal, and when the stereotyped motor performance of reflex grasping and of climbing was still dominant.

*Unilateral ablations*

In the following experiments, unilateral cortical ablations were made on 5 infant rhesus monkeys, during the fourth week of life. Three of these animals (Expts 1, 4 and 5) are reported also under *Bilateral ablations* following removal of tissue from a second hemisphere at the age of 6 months or more.

*Experiment 1*—Ablation of left motor and premotor areas on 21st day of life, transient contralateral weakness without spasticity, outward prehension until 2nd operation at 6 months [Infant series, no 1]

The subject of the experiment was an infant born in the Laboratory of a *M. mulotto* mother, November 27, 1933. (Mentioned previously in preliminary report as Premotor Series, no 28<sup>c</sup>) In the third week of life it showed, before operation, marked reflex grasping in all four extremities, together with the ability to climb and to walk slowly and unsteadily.

*Operation (Dec 18, 1933)*—On the 21st day of life the left motor and premotor areas were ablated (excluding the face areas, motor and premotor)

*Postoperative notes 1st day*—The animal was well recovered from the operation and walked and climbed surprisingly well. The following differences between the right and left extremities were seen: the left were moved more often and more accurately than the right, there was some weakness of grip on the right, but forced grasping seemed as strong on this side as on the left, the right extremities were slightly more extended than the left. There was no increase in resistance to passive manipulation. It was then returned to its mother, and clung in the normal manner.

*9th day*—The infant was again removed from the mother and examined. The motor performance seemed in every way identical on the two sides. There was no postural difference, and the right hand and foot were used as quickly, as often and as accurately as the left. Bilateral forced grasping was still present but less marked than at the previous examination. General motor conduct had become slightly more intricate with the growth of the infant.

*56th day*—Forced grasping had disappeared on both sides. Motor performance was

much more highly developed, but still did not reach the degree of skill and accuracy of the adult macaque. With increase in dexterity of the hands for finer movements a difference between the right and left became noticeable. Although general behavior seemed equal on the two sides, on walking, the right arm and leg were occasionally raised higher than the left with the right hand everted and extended; the right hand was not used as often as the left for prehension, and the fingers of the right hand were not used quite as well as those of the left.

*6th month.*—The above differences were still discernible, and it was noted that the slight overstepping of the right and the preference for the left hand were increased by fatigue. Resistance to passive manipulation was not increased on the right. A second ablation was then performed (See below *Bilateral ablations*, Expt. 1, cont.).

The motor deficit resulting from removal of all the motor regions of one hemisphere in this infant was slight both immediately following operation and as growth proceeded. The changes immediately after the operation consisted of a weakness and tendency to use the affected extremities less than those of the normal side. At the end of six months a slight postural hyperextension and eversion of the extremities were present, together with a tendency to use the normal hand more than the affected one; there was also an awkwardness in manipulating the fingers of that hand. Spasticity did not appear. Neither the degree of paresis, nor the spasticity seen in this animal was at all comparable with that which occurs after a corresponding lesion in the immature macaque or in the adult in which conspicuous and enduring spastic paresis develops following a similar ablation.<sup>5</sup>

The next experiment was carried out to compare the effects of a lesion of areas 4 and 6 with that following ablation of the entire frontal lobe.

*Experiment 2.*—*Ablation of left frontal lobe on 28th day of life; deviation of head and eyes to left, slight weakness of right limbs without spasticity; fine movements of digits still lost at 6 months (2nd operation).* [Infant series, no. 5]

The subject of the experiment was a *M. mulatta* born April 23, 1937. At four weeks it still retained its infantile grasping and sucking reactions, much as did the previous animal.

*Operation (May 21, 1937).*—On the 28th day of life, the entire left frontal lobe was removed under ether anesthesia (i.e., all tissue rostral to the sulcus centralis).

*Postoperative notes. 5th hour.*—Within 5 hours of the operation the motor status was as follows: the head and eyes were deviated toward the left, there was slight facial asymmetry and the left extremities were moved more quickly and spontaneously than those on the right; rhythmic progressive movements were made equally well on the two sides. Except for head turning, there was little abnormality in posture save that the fingers of the right hand tended to flex and curl under slightly more than those of the left.

*30th day.*—The deviation of the head and eyes had disappeared; motor coordination had improved and the infant was beginning to use its hands for feeding. It was then to be seen that the left hand was used more quickly and more accurately than the right. There remained, under excitement, a trace of turning of the head and eyes. Thumb sucking, in this as in other animals, was an indication of motor performance: a thumb sucker since birth, this animal sucked only its left normal fingers after the operation; when restrained in this, it attempted to suck the right thumb, but since the right fingers all moved together, it was impossible to place a single digit in the mouth.

During the ensuing four months prior to the second operation, the monkey showed little further recovery. Resistance to passive manipulation was not increased on the operated side.

The motor deficit resulting from removal of the entire frontal lobe in this infant consisted principally of its tendency to use the normal rather than the paretic extremities—particularly in thumb sucking; fine movements of the

affected fingers were less well performed than normal. There was also a slight postural difference between the fingers of the two sides, but no spasticity. The motor performance of the first few weeks was markedly altered because of the deviation of the head and eyes. Indeed, comparison with Experiment 1 indicates that there was no significant difference in motor performance between the two, except for the deviation of head and eyes in Experiment 2, due to inclusion of area 8 in the ablated tissue.

In the next experiment only the motor area (area 4) was removed.

*Experiment 3—Ablation of left area 4 on 26th day of life, slight postural change on right disappearing in 10 days, no other disability, 2nd operation at 6 months. [Infant series, no 13]*

This infant was born of *M. mulatto* parents on May 12, 1937, and developed normally. *Operation (June 7, 1937).*—The left motor area (area 4 alone) including face area was removed on the 26th day of life.

*Postoperative notes*—As the animal came out of ether, it was noted that, "when it vocalizes and struggles all four extremities are moved spontaneously in contrast to the movement following area 4 and 6 extirpations which is ipsilateral only. The movements of the right extremities are far less accurate and more extended than those of the left."

*1st day*—There was some eversion of the right hand and foot, but posture in standing, running and walking was otherwise normal. Forced grasping was slightly more intense on the right than on the left. Spontaneous movements were as numerous and as rapid on the right as on the left side.

*10th day*—Motor performance of the two sides seemed equal. Pasture was normal, fine movements were well performed with both hands, and the right thumb was sucked as often as the left. Performance at this stage was still infantile in that the animal fed itself by moving its mouth to the food without the use of either hand. From that time on no difference between the extremities of the two sides was detected. Placing and hopping reactions were bilaterally present.

Ablation of the motor area alone in this infant caused only a temporary motor deficit, consisting of a slight inaccuracy of movement on the right, and some postural asymmetry. There was spontaneous movement on the right, which at all times was as great as on the left. Ten days after operation no difference could be detected between the two sides, and thereafter fine movements were as well performed on the right as on the left. Placing and hopping reactions were bilaterally present. The deficit here was much less severe than in those animals in which the premotor area had also been ablated, and it was less severe than in the adult after ablation of area 4, in which paresis, particularly of the fine movements of the hand, persists indefinitely.

It was thought that in the previous types of operation, dissection of the motor regions might not have been deep enough to remove all Betz cells and that functioning motor cortex might remain. For this reason in the next infant, the postcentral gyrus (areas 3-1-2 and 5 of Brodmann), as well as areas 4 and 6 were included in the block removed, care being taken to cut well below the central sulcus.

*Experiment 4.—Ablation of left motor, premotor and parietal regions on 18th day of life, weakness, awkwardness and eversion of right extremities without spasticity, residual impairment of digital movements at 7 months (2nd operation). [Infant series no 4]*

This infant *Mococa mulatta* was born August 12th, 1936.

*Operation (Aug 30, 1936).*—In the third week of life, the left motor, premotor and parietal areas (areas 4 abc and 3-1-2).

*Postoperative notes.*—Immediately following operation there was no greater change in the performance of the contralateral extremities than that which appeared in previous experiments after removal of motor and premotor areas alone. No differences were evident between the extremities of the two sides when climbing, but, as in the preceding animals, it exhibited on the right some postural changes, and overstepping when progressing on a flat surface. It had acquired the habit of sucking its thumb, but, after operation, sucked the left thumb only, and that constantly for the next six months. No sensory deficit to touch or pain could be demonstrated. With the appearance of more intricate behavior patterns the motor deficit on the right became more marked; awkwardness of the right hand in picking up objects, occasional overstepping and missing of aim with the right extremities were noted. Resistance to passive manipulation was the same on the two sides. At 7 months the remaining motor, premotor and postcentral regions were extirpated (see *Bilateral ablations*, Expt. 4, cont.).

Ablation of the left motor, premotor and parietal regions in this infant was followed by (i) some awkwardness in the use of the right extremities, (ii) a tendency to use the fingers of the normal hand in preference to those of the abnormal, (iii) overstepping and dysmetria of right extremities—a symptom which increased in severity with the appearance of more intricate behavior patterns. There was no increase in resistance to passive manipulation.

Comparison of the protocols of the present animal and two others with a similar ablation suggested that the infants having postcentral ablations in addition to motor and premotor, showed slightly greater deficit than did those with lesions of areas 4 and 6 alone. The difference is, however, inconsiderable but the overstepping and awkward use of the hands were noted more often when the postcentral regions were also removed.

*Experiment 5.*—*Left hemispherectomy on 28th day of life; slight right hemiparesis without spasticity; deviation of head and eyes toward left; residual tendency to circle toward left and use left hand for skilled acts.* [Infant series no. 17]

This infant *Macaca mulatta* born June 29, 1937, showed in the third week of life a little more highly coordinated type of behavior than was present in other infants at this age. Voluntary grasping of objects had appeared and walking and running were fairly rapid, although still executed with less skill than that shown in adult behavior.

*Operation (July 29, 1937).*—In the fourth week of life the entire left hemisphere was removed under ether anesthesia.

*Postoperative notes. 1st day.*—By the end of the day walking and eating were well carried out. Movements on the left were quicker and more accurate than on the right. Forced grasping, still present before the operation, was marked on the left and diminished on the right. Groping and clinging were excessive. There was extreme deviation of the head and eyes to the left which was accentuated by excitement or interest.

*2nd day.*—It could feed and care for itself. Circling was prominent and sensory deficit could be shown by a difference in response to touch of one as compared with the other side of the body, and by the fact that in walking, the right extremities assumed bizarre postures sometimes getting "lost" and tangled in the cage bars. There was no increase in resistance to passive manipulation of either side. The right extremities were often held more extended than the left. A curious cat-like crouching gait developed in this as in another hemidecorticate infant, and all motor progression was slowly and cautiously undertaken.

*30th day.*—Some circling toward the left remained. The right hand was used less often than the left, the right extremities were occasionally hyperextended with "overstepping" on rapid progression or with fatigue. Placing and hopping reactions were absent on the right. There was no spasticity and motor coordination was in every other way equal on the two sides.

*Eight months after operation* this motor status was unchanged. The right motor and premotor areas were then removed. (See *Bilateral ablations*, Expt. 5, cont.)

This hemidecorticate infant showed, following operation, a tendency to use the left (normal) hand more than the right, and some hyperextension of the right arm and leg. The right hand could be used for fine movements, but not as well as the left. Movements were slower than is normal, and there was a crouching gait, but no spasticity; deviation of the head and eyes and turning were present throughout the first month, although these symptoms gradually diminished in intensity. Again, differences noted between the effects of different lesions were slight. Comparison of the protocols of this animal and a second hemidecorticate infant with those of animals having smaller lesions indicate that there is a trifle more overstepping in the hemidecorticate and a little longer duration of symptoms than in infants with area 4 and 6 lesions, or in those with the added postcentral ablation

### *Bilateral ablations*

In the four following experiments the results of bilateral cortical ablations are described. In each instance the first extirpation was made upon an infant monkey during the third week of life; the tissue was removed from the opposite hemisphere at a second operation during or after the sixth month of life.

*Experiment 1 (cont.)—Ablation of right motor and premotor areas at 6th month, great increase in motor deficit with spasticity, serial ablation of right and left frontal areas in 4th year, increase of spasticity and awkwardness after each operation [Infant series no. 1]*

At the age of three weeks, the left motor and premotor areas had been removed from this infant (see p. 479). At 6 months the residual changes consisted of a tendency to use the contralateral extremities less than the ipsilateral for fine movements, and a tendency to overreach with the right extremities.

*Second operation (May 28, 1934)*—At 6 months the remaining (right) motor and premotor areas were removed (Fig. 2).

*Postoperative notes 1st day*—The motor deficit was great on both sides, but greater on the left than the right. The animal was able to walk and feed itself, all movements were slow, but walking and climbing were well performed. Forced grasping, absent since the second month of life, returned and was greater on right than on left. Voluntary prehension was possible on the right but not, at this time, in the fingers of the left hand. The posture on the left was more in extension than normal and with excitement or fatigue this difference increased and the abnormal movements became exaggerated. The tendency to cling and climb, present in the infant, returned and persisted for many months. The animal walked on a broad base.

*1st week*—Improvement in motor coordination was great. Running, walking and climbing were well executed, although not as rapidly nor as skilfully as in the normal six-months infant. The left extremities were more extended than the right, and there was some increase in resistance to passive manipulation on both sides. The fingers were not used for feeding although both hands could grasp small objects.

*3rd week*—The hands were used in feeding, the tendency to climb and hang persisted and the slight hyperextension and spasticity remained.

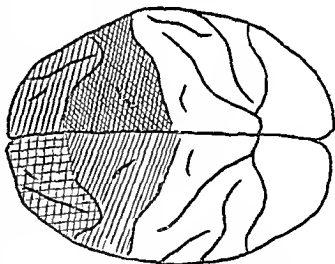


FIG. 2 (Expt. 1) Diagram of cerebral cortex of *Macaca mulatta* showing the four ablations made on Expt. 1



*7th week.*—No change had been observed; forced grasping could still be brought on and at this time the ability to jump long distances and to spring in the air, which later became prominent parts of behavior, were first noted.

*8th week.*—The protocol reads: "The motor performance has improved markedly. It runs more quickly and moves more accurately. Climbing is performed in the normal way, but performance on a flat surface is now almost normal. There is still a noticeable awkwardness in manipulating fine bits of food which seems to be equal in extent in the extremities of both sides." The animal's ability to groom at this time is shown in Fig. 3.



FIG. 3. (Expt. 1.) Infant macaque following bilateral ablation of areas 4 and 6, showing "flea-picking" act (grooming).

This animal was observed in the Laboratory for three years during which time, lacking motor areas in both cerebral hemispheres, it was able to perform ordinary cage activities and to grow and mature. During this time the motor deficit became a little more pronounced.

*3rd year.*—The following abnormalities were noted: Posture of the extremities in walking and running was "spastic," i.e., extremities were held more rigid, hands and feet were everted, overstepping was seen; all movements were slower than normal; the tendency to cling and climb had remained; in feeding the finger movements were less accurate and less discrete than normal.

*Third operation (Mar. 5, 1937).*—The remainder of the *right* frontal lobe (areas 8-12) was removed (Fig. 2).

*Postoperative notes.*—Following this procedure the disability in the extremities became much more marked on both sides, but it was greater left than right. The legs became as rigid as poles, and conspicuously everted. The left hand was not used for feeding and the right was used awkwardly and not until the third postoperative week. Turning of the head and eyes, and circling toward the side of the lesion also appeared, presumably due to removal of area 8. All motor acts were carried out slowly and for a time after the operation the animal showed such a high degree of hypokinesia and apparent confusion, that, for several days, it had to be fed by pouring liquids into its mouth.

*6th month.*—The confusion had entirely disappeared by the end of the ensuing six months, but there had been little improvement otherwise. Climbing and clinging were prominent. Resistance to passive manipulation, especially flexion, was intense at all joints.

*Fourth operation (Nov. 18, 1937).*—The remaining left frontal areas 8-12, were then removed. Following this, the spasticity and tendency to climb and cling were unaltered,

as was posture, but the left hand was used somewhat better than the right; the right extremity, indeed, showed, for a time, no voluntary movement whatsoever, and hypokinesia became extreme. The animal would not move for days after the operation, except when grossly stimulated. It made no attempt to feed or swallow, so that feeding by stomach tube became necessary for a time. During the succeeding 8 months there was gradual recovery and speed of reaction slowly increased. It became able to feed itself and to pick

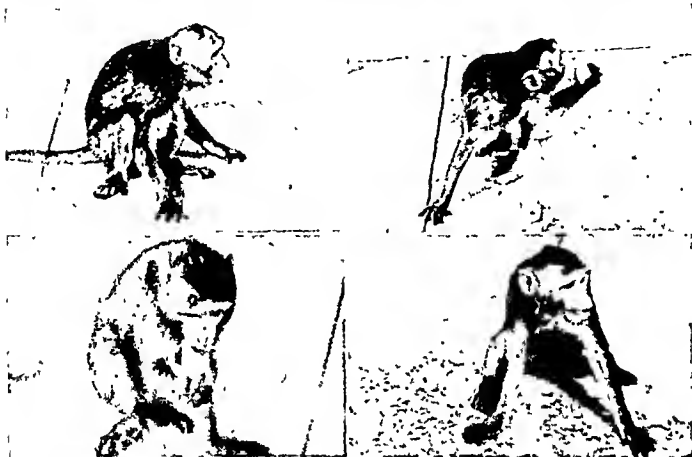


FIG. 4. (Expt. 1.) Enlarged photographs of macaque from moving pictures taken Dec. 4, 1937 after removal of all frontal lobe tissue, showing posture and use of hands.

up objects with either hand (Fig. 4). The spasticity and bizarre posture with rigid extremities remained. All movements were exaggerated and poorly coordinated. This animal is still alive (October, 1938) at the age of almost five years. It is now a mature female in excellent nutritional state and with normal menstrual cycles, able to feed itself and exist in a cage in spite of extreme motor disability. It feeds by bringing its face down to a pan in which food is placed. When excited it springs wildly in the air, usually falling on its back, and for the rest of the time is found clinging solemnly to the bars of the top of its cage.

Extirpation of the remaining motor and premotor tissue from a six-months-old macaque, from which one motor region had previously been removed at three weeks, was followed by marked bilateral increase in motor disability, greater on the side contralateral to the second operation; it consisted of inability to perform fine movements of prehension; there were also postural changes involving hyperextension and eversion of the extremities and moderate increase in resistance to passive manipulation. The subsequent extirpation of the remaining tissue from first one and later the other frontal lobe produced, after each operation, a great increase in the above deficits, together with hypokinesia, deviation of the head and eyes and a seeming apathy and confusion.

*Experiment 4 (cont.).—Ablation of right motor, premotor and parietal regions during 7th month; bilateral spasticity and postural changes; "scissors gait" and contractures. [Infant series no. 4]*

The changes in motor status ensuant upon ablation of the left motor, premotor and postcentral regions are reported above (p. 481). During the 7th month a residual impairment of the fine movements in the right extremities remained.

*Second operation (Mar. 17, 1937).—The second (right) motor, premotor and parietal regions (areas 6a upper part, 4abc, 3-1-2 and 5) were then removed (Fig. 5).*

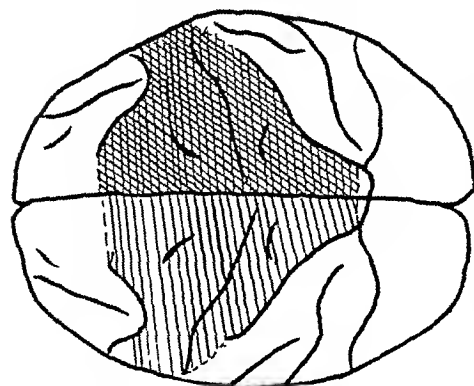


FIG. 5. (Expt. 4.) Diagram of cerebral cortex of *Macaca mulatta* showing areas extirpated in Experiment 4.

ive days, but resistance to passive manipulation had increased especially on the left. The hind legs were beginning to be flexed and adducted, necessitating a "scissors" gait, later extreme. There followed a gradual intensification of spasticity and bizarre posture.

*2nd month.*—The hind legs had become greatly scissored (Fig. 6), the hands were used little in feeding and an enormous exaggeration of all motor response, as in jumping, or in the startle reaction to fear, appeared.

*First year.*—The notes record a gradual augmentation of the disability due to development of contractures and of an intense degree of spasticity. The animal now (August 1938) climbs and clings rather more than a normal monkey of its age. It walks with exaggeration of all movements and springs enormous distances (6 to 8 feet) having little control over the extent of its motor response. It feeds itself, usually reaching with its mouth for food, although either hand may be used for prehension. Individual movements of the fingers are not demonstrable.

Bilateral ablation of motor, premotor and parietal regions in this animal was followed by a severe motor disability. Although the animal could walk, climb and feed itself, gait and posture were grossly altered. Spasticity was conspicuous together with contracture, scissors gait and great limitation of the movements of the fingers. The disability in this animal and in two other infants (baboons) following the removal of the same areas, was far greater than that which results from the bilateral removal of the motor and premotor areas. The adductor spasm and scissors gait were characteristic of all three of these animals and of no others in this series with lesions elsewhere.

*Experiment 6.*—Ablation of left motor and premotor areas during 4th week of life; residual slight awkwardness in use of fingers. Right hemispherectomy; bilateral spasticity, forced grasping and circling toward the right. [Infant series no. 7]

*Postoperative notes. 1st week.*—During the week following operation adequate motor performance developed: running and walking were moderately rapid, but they were executed on a wide base and with greater extension of the left than of the right extremities. There was a slight increase in the tendency to climb and cling, and forced grasping, although difficult to induce, was demonstrable once the animal grasped an object, it had difficulty in releasing its grip. There was a minor increase in resistance to passive manipulation of the limbs and the right hand was used for feeding. The animal tended to "lose" its limbs, particularly those of the left side, so that they became entangled in its bedding and in the bars of the cage. It stopped sucking its thumb, since it was unable to place the thumb in its mouth.

*10th day.*—Bilateral deficit was still present as it had been during the first postoperative

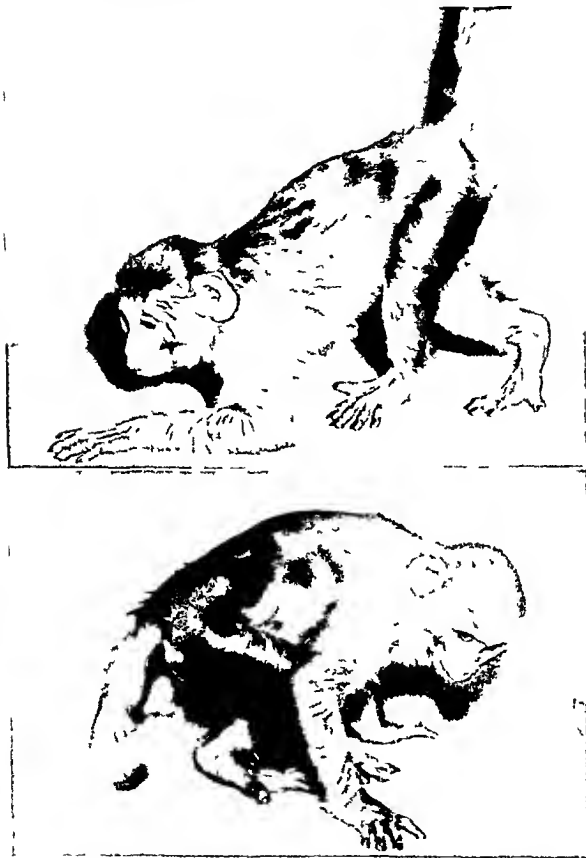


FIG 6 (Expt 4) "Scissors gait" appearing after bilateral ablation of motor, premotor and postcentral regions

Removal of the left motor and premotor areas from this infant, born April 5, 1935, during the fourth week of life was followed by minimal motor disturbance, such as is described in Experiment 1. A year and a half later the animal showed normal posture and cage behavior with no spasticity and with reflexes equal on the two sides. It tended to use the left hand more than the right and placing and hopping reactions were absent in the right foot.

*Second operation. (Sept. 30, 1936).—*The right hemisphere was then removed in its entirety under ether anesthesia (Fig. 7).

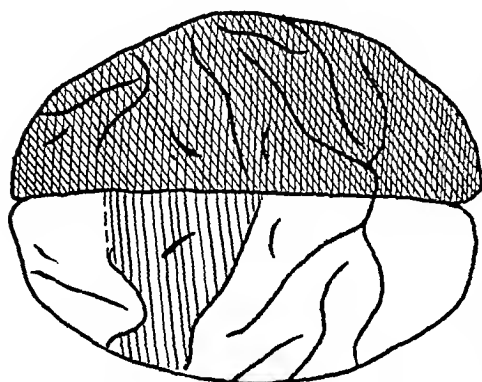


FIG. 7. (Expt. 6.) Diagram of cortex of *Macaca mulatta* showing regions extirpated.

*Postoperative notes. 1st day.*—The animal was able to right itself and stand and walk. There was bilateral motor deficit, but its behavior was more nearly like that of a hemidecorticate adult than an animal with bilateral motor and premotor area ablation. It circled always toward the right and ate food carried to its mouth by the observer. All four extremities exhibited increased resistance, the left more so than the right, and there was more resistance on flexion than on extension. Forced grasping had also reappeared, and was greater on right than left; all movements were slow and uncertain. Eating was done rapidly and quite automatically, chewing at times continued after all food was swallowed; at other times food was held indefinitely in the mouth. Placing and hopping reactions were everywhere absent.

*1st week.*—Speed and accuracy of movement were slightly increased, but the type of performance was unchanged. Forced grasping and circling toward the right were so extreme that purposefully directed movement was almost totally prevented. The hands were never used for voluntary prehension.

*1st month.*—The pattern of motor acts was again unchanged, except that some increase in speed of movements had once more taken place.

The removal of an entire hemisphere after previous ablation of motor and premotor areas was followed by a profound, although not totally disabling, motor deficit. Residual motor function enabled this animal to stand, walk and eat, but spasticity and the loss of coördinate movements of prehension prevented the performance of all the fine motor acts. The deficit was greatest on the side opposite the hemispherectomy and the disability was extreme. The alteration in motor performance in this animal, from which the major part of the remaining cortical tissue was removed when aged a year and a half, was more extreme than in any other animal in this series following any lesion, (Fig. 8). It never regained prehension up to the time of its death six weeks after the second operation. The extremities contralateral to the *second* operation, the hemispherectomy, were the most disabled.

*Experiment 5 (cont.).—Left hemispherectomy during 3rd week of life; residual overstepping and awkwardness of right fingers. Ablation of right motor and premotor areas in 6th month; marked bilateral motor deficit, greatest on right, with spasticity, eversion of extremities, and awkwardness in prehension. [Infant series no. 17]*

The changes in motor performance ensue upon left hemispherectomy in this infant are described above (p. 482). Seven months after this first operation there was no spasticity and no postural or motor deficit, except for slight awkwardness in the right fingers, and some overstepping on the right side.

*Second operation (Mar. 4, 1938).*—The right motor and premotor areas were then removed (Fig. 9).

*Postoperative notes. 1st day.*—The animal walked and fed itself. Marked deficit was present in the motor behavior of all four extremities. *This was much greater on the right, ipsilateral to the recent operation;* thus the note says: "Yesterday, before the second opera-



FIG. 8. (Expt. 6.) Characteristic posture of *Macaca mulatta* and brain of same animal photographed at autopsy showing lesion of motor and premotor areas on the left and the hemispherectomy on the right.

tion, the deficit in the extremities due to the left hemispherectomy had practically disappeared. Today this deficit has almost completely reappeared and the animal on first inspection has the appearance of an eight-months infant which has had only a left hemispherectomy. Head and eyes are once more *deviated to the left* and the animal circles to the left, as it did after the first operation. Motor progression is slowly and clumsily done,

but the right extremities are more extended than the left. The left hand is used in preference to the right." There was no spasticity, and hopping and placing reactions were absent on both sides.

*2nd day.*—Motor progression had improved but was still slow and incoördinate, the right arm and leg being more extended than the left and less manageable. Feeding was usually done by approximating the mouth to food, but the left hand assisted frequently by shoving and grasping loose bits.

*1st week.*—The left hand was well used for feeding. Gait was described as "rocking" and on a "broad base" with the tendency to hop, jack-rabbit fashion, instead of running. There was slight increase in resistance to passive manipulation, equal on the two sides.

*4th week.*—Speed of movement had increased, but posture was still grossly abnormal. The left hand was used in preference to

the right but the right could also now be used at times. On both sides, the fingers were moved awkwardly and all together. Deviation of the head and eyes had disappeared.

This animal continues (August 1938) to maintain an adequate existence with two other animals in the cage, being able to run (Fig. 10), feed, climb and play, although obviously lacking a normal smoothness of coördinate motor performance. Chiefly noticeable are the tendency to walk on a broad base with extension, and the eversion of hands and feet. The left hand continues to be more accurate than the right; resistance to passive manipulation is only moderately increased and is equal in the two sides.

Spasticity, increase in extensor posture, and marked limitation of finer finger movements appeared after extirpation of motor and premotor areas secondary to a hemispherectomy. The deficit was greatest on the side opposite the first operation of hemispherectomy. The second operation reproduced the deviation of the head and eyes toward the *side of the first operation*. In this animal, as in the preceding one, the greatest motor deficit was on the side opposite the hemispherectomy. The total deficit was far less than in the previous animal from which the hemisphere was removed as an adult. Thus, degree of deficit in these two animals has specifically to do with age at the time of operation. In an adult, in contrast, severity of paresis is always directly related to the brevity of the interval following operation; and the side opposite the most recent lesion is always the most profoundly affected.

## DISCUSSION

It has long been recognized that cortical lesions made on young animals have less effect on behavior than have similar lesions in adults of the same species. In 1866, Vulpian,<sup>12</sup> discussing hemidecortication, advised the use of

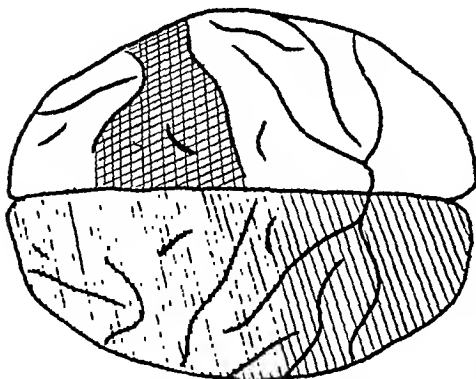


FIG. 9. (Expt. 5.) Diagram showing left hemispherectomy and ablation of motor and premotor areas.

young animals since "they stand the procedure better . . . than do adult animals" (p. 677). In 1875 Soltmann<sup>10</sup> found that puppies deprived of one hemisphere develop a highly coordinated motor performance with little difference between movements of the two sides. And in man it has been consistently observed following birth injuries, or other congenital deficiency of brain tissue, that the degree of motor paresis is often small when compared with the effects of a similar lesion in adults. Tsang<sup>11</sup> has recently found that the ability of



FIG 10 (Expt 5) Showing posture of 7 months old *Macaca mulatta* following ablation of left hemisphere and of right motor areas

adult rats to solve mazes following cortical ablations is proportional to the amount of tissue removed, but that the rat operated upon in infancy will show the same degree of deficit in performance after removal of 50 per cent of cortical tissue, as does the adult following removal of only 7.4 per cent.

The experimental data presented in this paper amply confirm this striking quantitative difference between restitution of motor function in the adult and in the infant animal. Two regions in the central nervous system may be regarded as capable of mediating motor function in the absence of the true "motor" areas: (i) the other areas within the cortex, or (ii) subcortical "centers." At the time of the primary ablation motor function in these infant macaques must be chiefly subcortical, and it might be supposed that in the absence of the higher motor areas these older centers would then develop more complex motor patterns. It is possible that they do, yet the present indi-



cate that the more complex motor performance of the infant as compared with the adult, which develops in the absence of motor areas, is mediated chiefly through other regions of the cerebral cortex.

In the adult the chief cortical motor projections influencing an extremity originate in the motor and premotor areas of the opposite hemisphere. The ipsilateral motor and premotor areas are known to affect motor performance and since there is also slight but definite recovery after removal of all motor and premotor cortex, contralateral regions other than areas 4 and 6 may also exert some influence. But, since, in the absence of areas 4 and 6, the performance of the adult is little more complex than that of the infant, in which cortical influence is minimal, the effector pathways of the cortex in the adult must be limited chiefly to the motor and premotor cortex; and residual motor performance after their ablation must be due largely to subcortical centers, as in the "thalamic" animal.

The chief motor pathways from the cortex of the young animal also come from the contralateral motor areas. However, in their absence motor performance develops to almost normal limits in the growing and developing animal (Expts. 1, 3 and 6) and ablation of the motor areas from the ipsilateral side will then produce motor deficit about equal on the two sides (Expts. 7 and 8). Thus, in the absence of contralateral "motor" areas, the ipsilateral "motor" regions of the infant become more effective than those of the adult. Similar influence can also be seen in the non-motor regions where tracts from frontal association and postcentral regions of the infant may have an important influence on motor performance (Expts. 1 cont., 5 cont., and 6). The influence of the postcentral regions is obvious from Experiment 4 in which following bilateral removal of motor, premotor and postcentral areas greater motor deficit appeared than in animals with motor and premotor ablations only.

#### *Time of onset of motor function in the cortex*

The motor and premotor areas of the three-weeks-old infant clearly participate in reflex motor acts since: (i) their removal results in definite, though slight, alterations in performance; (ii) removal of the motor area alone produces less change; while (iii) removal of other areas, such as the occipital lobes, have at this age no effect on motor status. (The latter observations were made on two infants operated upon for another purpose, and not included in this series.)

However, during the third week of life, motor performance is evidently largely subcortical. It is of simple and limited pattern, chiefly composed of automatic components such as grasping. It is only slightly affected by cortical lesions which in older animals produce greater effect, and, with the later appearance of more intricate patterns of performance, the deficit becomes intensified; that is, as the cortical type of performance becomes dominant, the increase in deficit, though small, is manifest. Stimulation of the motor area in these 15 animals produced motor response in only 9. The responses

differed from those of the adult in that a stronger stimulus was required to produce movement, and the movement was always generalized *i.e.*, the entire limb or side, rather than the discrete response of a finger, or joint, characteristic of stimulation of area 4 in the adult. Soltmann<sup>11</sup> reported these same differences on stimulation of cortices in young and adult cats and dogs.

Physiological evidence indicates that conjugate movements of the eyes and head turning are early under cortical control. In the adult, after lesions of area 8 in the frontal lobe, deviation of the head and eyes, and consequent circling in progression develop. The same result is obtained after lesions in the infant, and, in contradistinction to the results of lesions elsewhere, it is a severe and enduring change which closely approaches the corresponding paresis of an adult. In Experiment 5 the transient head and eye deviation toward the side of the lesion (left hemispherectomy) was reproduced six months later, and *in the same direction*, by extirpation of the contralateral areas 4 and 6 which in the adult have no effect on eye movements.

### *Anatomical correlations*

Since many of the animals in this series are still alive and histological material is not yet complete, a detailed correlation of anatomy and physiology will be reported later. The relation of the development of function with myelination is still uncertain, although in all vertebrates it is agreed that fully developed motor coördination appears only with myelination. Artom<sup>1</sup> has observed myelination in two macaques, one new born and one three weeks of age, and has compared his findings with those of Mingazzini in a baboon of three weeks. In none were the corticospinal tracts myelinated. The present data fit well with two theories discussed at length by Langworthy,<sup>7</sup> namely, that myelination occurs in proportion to use, and that, as it starts nearest the cell bodies, the shorter axons are complete first. The relatively high degree of functional activity of the cortical eye center as compared with those of the limbs would thus be explained, for shorter tracts in organs such as the eyes which are used early are here involved.

The histological structure of the cortex is consistent with the existence of motor function in postcentral and frontal association areas; for in the postcentral region Betz cells and other large motor cells appear in the fifth layer and in the frontal areas. Area 8 and the caudal part of 9 contain a motor type of cell, although smaller than those of the postcentral areas. In the infant, the cortical layers are less well differentiated as are the individual types of cell, a factor which may be correlated with the lessened specificity of function of the cortex at this age.

### *Neurological changes*

*Spasticity.* The problem of the development of spasticity or of increased resistance to passive manipulation is of interest. In general, rigidity and spasticity were absent up to 6 months of age after unilateral lesions made in in-

fancy; a second lesion of the opposite hemisphere caused immediate though moderate increase in resistance bilaterally. This gradually increased over a period of months as the animal grew older. The rigidity was extreme, and followed by contractures in three animals having bilateral removal of motor, premotor and postcentral regions, and in the animal with all the frontal lobes of both sides removed. This late development of rigidity may in some way be related to the phenomena fully discussed by Langworthy<sup>6</sup> although appearing at a different age, namely, that young animals (kitten, guinea pig and opossum) when decerebrate, do not develop rigidity, but show extreme hyperactivity and rhythmic progressive movements. Later, at a time which correlates roughly with myelinization, decerebration will produce rigidity in the same species. The hemiplegias of young human infants are not, in general, as spastic as are those of adults, but little is known about the intensity of this factor in relation to age in man.

*Posture.* The stance and posture of these animals following various extirpations was so constant as to merit mention; their interpretation would be more difficult. Three types were seen: (i) the hemidecorticate infant without spasticity or limb asymmetry walks like a stalking cat, slowly and cautiously, with shoulders low and forelegs slightly bent. (ii) The infant following bilateral ablation of the motor and premotor areas walks on a broad base with hands and feet everted, fingers and toes spread, and with slight overstepping. Additional removal of the frontal association areas accentuates this (Figs. 4 and 10). The animal then walks as if on poles with widely separated and extended legs. (iii) Add the postcentral gyri to ablated motor and premotor areas and a "scissors gait" is produced. Here there is extreme rigidity, with gross adduction and flexion of the hind limbs and some of the fore, although the hands remain everted, fingers spread (Fig. 6).

*Reflexes.* The absence of detailed notes on reflexes in the protocols of the infants is conspicuous and a result of the difficulty of examination and the equivocality of the results. An infant monkey, when not clinging, is nearly always struggling, so that even with unlimited time and patience, consistent findings would be impossible. Tendon jerks are difficult to evaluate in the adult monkey; in the infant, no significant differences were detected as the result of operation. The changes in reflex grasping could be watched, however, and definitely related to the development of voluntary prehension. The effect on forced grasping of the ipsilateral cortex is far greater in the infant than in the adult. *Placing and hopping reactions* were, in every case examined, abolished by motor and premotor ablation. In one case with bilateral ablation of area 4 alone, placing and hopping reactions still existed.

It is thus evident that the functional organization of motor activity in the central nervous system of the adult monkey may be greatly altered by the early removal of the motor and premotor areas of the cortex; it is clear also that in the absence of areas 4 and 6 other cortical fields may take over, in part, the integration of motor activity. Further study may bring to light the

anatomical and physiological factors which make possible in the infant nervous system this extraordinary reorganization of functional activity.

### CONCLUSIONS

1. The highly developed and coordinated motor performance which is present in the monkey deprived of motor and premotor tissue in infancy is due to integration from the other cortical regions, namely the frontal association areas and the postcentral regions.

2. The motor deficit under such conditions consists of a loss of the finer movements such as those of prehension.

3. Infantile patterns of behavior, such as reflex grasping, and a tendency to climb and cling are brought out by total ablation of the motor areas and persist indefinitely although voluntary purposeful behavior is also present.

4. Characteristic postures appear with specific lesions. With bilateral extirpation of motor and premotor areas, hyperextension and walking on a broad base appear. On addition of the postcentral gyrus to the above lesion, adduction and a scissors gait ensues.

5. Paresis of conjugate deviation of the eyes following lesions of area 8 is more severe and enduring in the infant, than is the paresis produced by other cortical ablations. It thus resembles more nearly the paresis produced in an adult by a similar lesion. It is suggested that this may be due to earlier myelination and functional development of these shorter tracts.

6. The concept that specific cortical foci have major functions in specific regions of the body, and in addition a minor influence on many other parts is not new, and applies to the adult cortex, but in less degree than to the infant cortex. The factor which makes possible the enormous difference in degree, however, is still to be explained.

I should like to express my thanks to Drs J F Fulton and C F Jacobsen for their advice and encouragement in this investigation, and to Dr Fulton, Dr Jacobsen, Dr Robert Dow and Mr Robert Malmö for assistance at operations

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# THE SUMMATION OF FACILITATING AND INHIBITORY EFFECTS AT THE MAMMALIAN NEUROMUSCULAR JUNCTION

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DURING progressive curarization, stages are reached in which excitation of voluntary muscle by a given nerve impulse may be either prevented or made possible through the after-effects left by earlier impulses. The nature and the number of these after-effects are uncertain. In the mammal there are three distinct phenomena to be accounted for, namely:

1. *Wedensky inhibition.* While isolated volleys of impulses are still able to excite the muscle, repeated stimulation of the nerve may at certain rates lead to a state of more or less complete junctional block. At low frequencies (6 to 600 per min.), the muscle responds more strongly to the first volley than to any following. Each volley of the series, whether transmitted or blocked, leaves an inhibitory after-effect which lasts at least 10 seconds. The higher the frequency of stimulation, the more profound is the final level of inhibition reached; but at tetanizing frequencies two or more volleys may be transmitted before any evidence of inhibition appears.

2. *A brief phase of facilitation.* When isolated volleys are blocked, two in rapid succession may still excite. The facilitating after-effect of the first volley is maximum at about 3 m.sec. (Bremer and Homès, 1932) but persists in some degree for 40 or 50 m.secs. Tetanic stimulation of the nerve, however, evokes only an initial twitch-like contraction. Junctional block then returns and remains as long as stimulation is continued at the same frequency.

3. *A second, more prolonged, phase of facilitation.* After tetanic stimulation of the nerve is stopped, the muscle is found to respond to single volleys timed a few seconds apart. This post-tetanic recovery is still demonstrable when curarization is so far advanced that the conditioning tetanic stimulus, however prolonged, fails to elicit any visible contraction (Boyd, 1932). For brevity, the underlying processes responsible for these three phenomena will be designated respectively  $I$ ,  $F_1$  and  $F_2$ , although it is not certain that the two last are distinct. Rosenblueth and Morison (1937) have suggested that  $F_1$  is a summation of two or more quanta of acetylcholin (ACh), released at the same nerve ending;  $I$ , a diminution in size of the later quanta of a series, such that they become inadequate to excite even by summation; and that  $F_2$  is a mobilization of potassium, released at the nerve endings.

None of these hypothetical processes has been definitely identified. In an earlier paper (Maaske, Boyd and Brosnan, 1938) evidence was given indicating that  $F_1$  is not a summation of quanta of ACh. Brown and von Euler (1938) hold that  $F_1$  and  $F_2$  are identical, the former being the mobilization of K ions

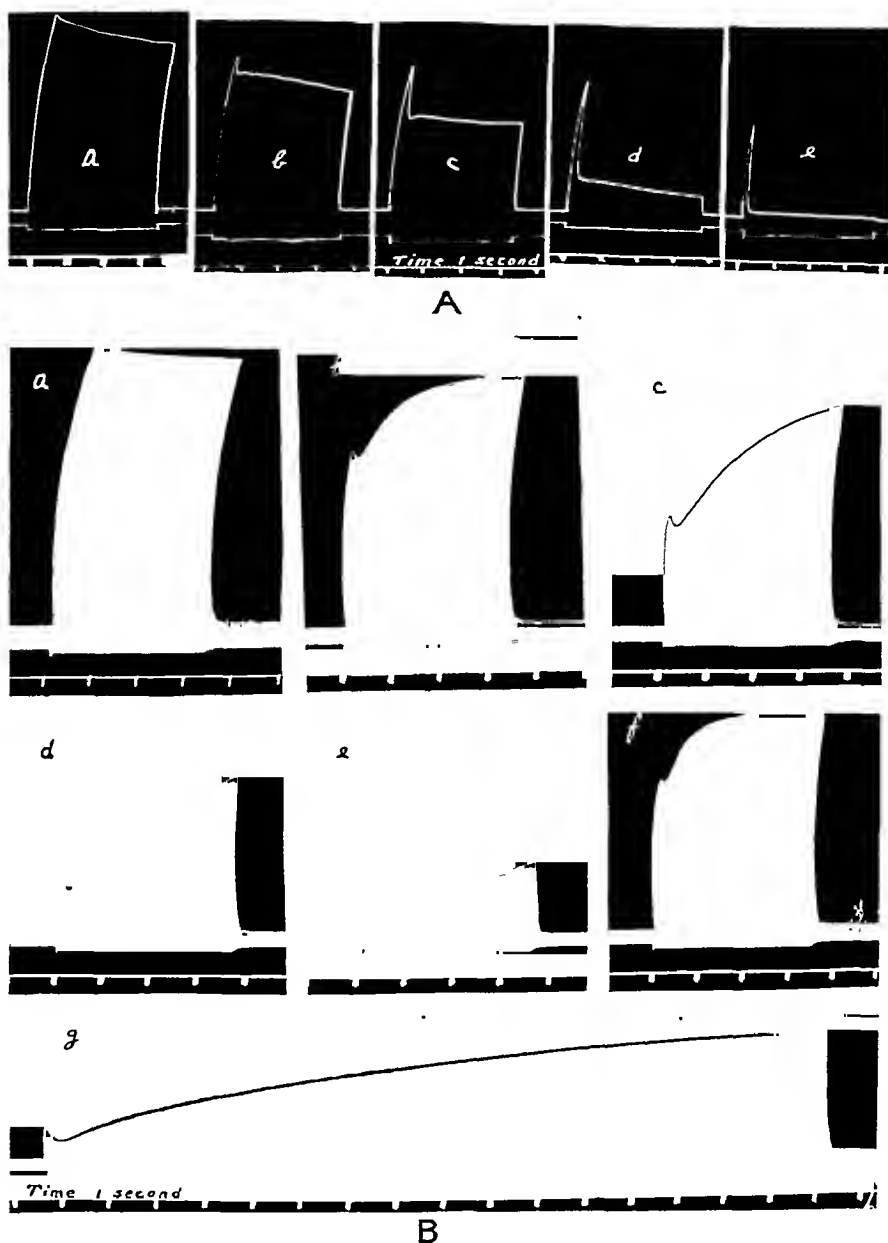


FIG. 1. A, dog, 12.6 kg., nembutal. Contractions of tibialis anterior in response to stimulation of motor nerve at frequency of 80 per sec., for successive 4-second periods. a, normal; b to e, during progressive administration of 21 mg. of crude curare.

B, dog, 15.9 kg., nembutal. a, normal tetanus; b to e, during progressive administration of 9.2 gm. of  $MgSO_4$ ; f and g recorded at same stage of depression as d. Frequencies, a to e, 80; f 120, g 40 per sec.

at the motor end plate by a single impulse, and the latter the same effect magnified by the arrival of a train of impulses in rapid succession. Brown and von Euler offer no explanation for the fact that the two phases of facilitation are separated in time. If the total mobilization of K ions continues to increase during tetanic stimulation of the nerve, the facilitating effect becomes masked, after the first two or three volleys, by some inhibitory factor; and the second phase of facilitation must then be accounted for by assuming that the inhibitory factor subsides with relative rapidity during rest, allowing facilitation to become unmasked again.

Certain facts appear to support this interpretation. Lubinska (1935) observed that during the progressive administration of a magnesium salt the muscle response to single volleys became weaker. When it had failed entirely, continued stimulation of the nerve at a frequency of 27 per sec. evoked a tetanus, gradually built up but well sustained. There was also a post-tetanic return of the single twitch response, maximum at first and subsiding over a period of several minutes. The entire sequence of effects suggests the continued summation of a single facilitating factor, removed during the post-tetanic period by some relatively slow process. In the paper referred to above (Maaske, Boyd and Brosnan, 1938), we showed that the facilitating after-effect of a single volley runs the same time course under Mg as under curare. The inhibitory effect, however, is, under Mg, comparatively brief and feeble. The inference is obvious that under Mg,  $F_1$  can be summated continuously throughout an extended series of volleys; and that under curare the discontinuity between the two phases of facilitation may be only apparent, and due to masking by  $I$ .

This paper presents some further observations on the course of junctional facilitation, both under curare and under Mg. It will be shown that under curare, facilitation is present, but masked, during the period of Wedensky inhibition. On the other hand, it will be shown that the building up of a tetanus under Mg is not continuous; it takes place in two stages, for which two distinct processes may be responsible.

#### PROCEDURE

Dogs and cats were used, anesthetized with nembutal (45 mg per kilo). The right leg was immobilized by drills through the tibia. Contractions of *m. tibialis anticus* were recorded on smoked paper, the muscle ordinarily being made to pull against a rubber band, but for the tetani shown in Fig. 1 a steel spring myograph was employed. The sciatic nerve was sectioned. All stimuli, except as otherwise stated, were applied to the peroneal nerve through shielded platinum electrodes, and were initially adjusted to a strength just above maximal for the motor fibers. Tetanic stimuli were delivered from a Harvard coil, or, when varied frequencies were desired, from a neon-tube circuit. The latter also served for test stimuli repeated at intervals of 5 to 10 sees. The desired stage of junctional depression was induced and maintained by slow inflow, either of  $MgSO_4 \cdot 7H_2O$ , in 6.7 per cent solution, or of crude curare, 0.1 to 1.0 per cent, from a burette connected to the left femoral vein. Eserine (physostigmine salicylate) was administered by the same route. In certain experiments the left iliac artery was sectioned and tied in order to permit injections of ACh or of KCl solutions through its central stump into the lumen of the aorta. In the experiments with curare artificial respiration was employed, with Mg it was not necessary.



## RESULTS

1. *Responses to tetanic stimulation of the nerve.* (a) *Curare.* Figure 1A (b to e) shows a series of tetani, each of 4 secs. duration, recorded during progressive curarization. The effects shown were described by Hofmann (1903) and these graphs are presented merely for comparison. The maximum tension is reached very early and is followed by Wedensky inhibition, which becomes more and more nearly complete as curarization deepens. The initial rise is meanwhile reduced somewhat in height, but its time course does not change appreciably. While the tetani shown were all recorded with a uniform frequency of stimulation of 80 per sec., the same general form of record is maintained with any frequency from 20 to 120 per sec. At any given stage, however, an increase of frequency improves the initial response, while the after-depression becomes more profound.

(b) *Magnesium.* Figure 1B shows a series of myograms recorded under conditions identical with those of Fig. 1A, except that Mg was substituted for curare. There is here also an initial abrupt rise of tension, followed by partial relaxation. The relaxation, however, is incomplete and transient, being recorded merely as a notch on the ascending portion of the myogram. It is followed in turn by a secondary rise which transcends the first.

Until the secondary ascent begins, these tetani are apparently identical with those of the curarized preparation. With increasing dosage of Mg the primary rise is reduced in height, but its time course does not change appreciably. The time course of the secondary rise is altered, the slope becoming more gradual. Figure 1B, g, shows such a secondary rise continuing for 15 secs. After the initial response has been completely suppressed by Mg, a feeble de-

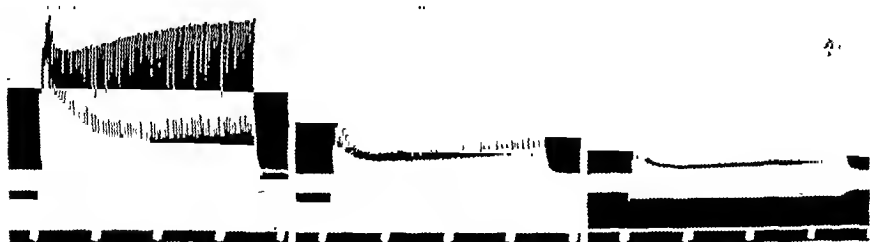


FIG. 2. Same preparation as in 1 B. Responses to stimulation of nerve at frequency of 20 per sec., during progressive administration of  $MgSO_4$ .

layed tetanus can still be built up by prolonged stimulation of the nerve. At any stage prior to this, an increase of stimulation frequency has the following effects;—a strengthening of both the primary and secondary responses, a steeper ascent for the latter, and a reduction, both in width and depth, of the notch separating them (compare *d* and *f* in Fig. 1B).

We have observed a notch, similar in magnitude and position to those shown in Fig. 1B, in myograms recorded from animals under nembutal alone. In these instances, however, as in those noted by Hofmann (1903) using ani-

mals under deep ether anesthesia, the notch was present only with relatively low frequencies of stimulation and disappeared with an increase of frequency. When the effects of nembutal and Mg are combined, the notch is present at all frequencies up to 120 per sec., although it does undergo the changes described above. A similar notch appears in some of the graphs of Lubinska (1935) although it is left without comment. At a frequency of 20 per sec., the secondary rise is barely perceptible, and never reaches the height of the primary. This type of response resembles, more nearly than any obtained with higher frequencies, a sustained Wedensky inhibition (Fig. 2).

The general form of tetanus shown in Fig. 1B is retained after Mg has completely suppressed any visible response to an isolated volley. Since the Mg block is reversible by the agents which are antagonistic to curare (Brosnan and Boyd, 1937) both components of the tetanus must involve a recruitment of units in the muscle rather than in the nerve. Superficially, the effect resembles that of small doses of eserine. Cannon and Rosenblueth (1937) find a similar "plus-minus-plus" sequence in the response of the nictitating membrane, in lightly eserinizied cats, to tetanic stimulation of the preganglionic sympathetics. These authors attribute the "minus" phase to accumulation of a depressing excess of ACh, and the second "plus" phase to a fall in concentration of ACh resulting from an assumed reduction in size of quanta. Such an explanation might equally well apply to the observations of Briscoe (1936) whose myograms, also recorded from eserinizied cats, closely resemble those shown in our Fig. 1B.

Under eserine, however, the transient depression is magnified by an increase in the frequency of stimulation (Briscoe, 1936). This is of course to be anticipated if an excess of ACh is the cause. Under Mg, as noted above, increase of frequency has just the opposite effect. For this reason, the notch in our myograms can hardly be attributed to the paralytic action of excess ACh. Moreover, the phase of depression in a tetanus recorded under eserine is abolished after small doses of Mg (Fig. 3).



FIG. 3. Dog, 8.8 kg., nembutal. Responses during three 4-second periods of stimulation of nerve, frequency 80 per sec.; at times indicated. Eserine (4.4 mg.) at 4:55. Same dose repeated at 5:11.  $MgSO_4$  (5 cc. of isotonic solution) at 5:00. Same dose repeated at 5:13.

It seems probable that the initial response to tetanic stimulation, under Mg, is due to  $F_1$ , the same factor which is responsible for the brief phase of facilitation under curare. The notch which follows may mean either the exhaustion of  $F_1$  or a transient masking by  $I$ . Similarly, the secondary rise may be due either to a second facilitating factor, requiring prolonged summation to become effective, or it may be due to continued building up of  $F_1$ . Obviously, under Mg a sustained decline in size of quanta of ACh either does not take place, or, if it does, there is no resulting impairment of junctional transmission.

2. *Post-tetanic effects.* We have previously reported (Boyd and Brosnan, 1936) that facilitation, following a given tetanus, lasts about as long under Mg as under curare; and that in both conditions the degree and the duration of the recovery vary with the number and frequency of the conditioning volleys. It seems probable, therefore, that the underlying factor ( $F_2$ ) is the same under Mg as under curare.



FIG. 4. A, cat, 2.7 kg., nembutal and curare. B, same preparation, after 2 mg. each of eserine and atropine, with additional curare to restore original state of block. Single test stimuli at 8-second intervals throughout, tetanic stimulation (Harvard coil, 1 minute) at signals. At arrow (B) 5 mg. of acetylcholin in 1 cc. saline injected into right iliac artery.

(a) *Curare.* Figure 4A shows a typical post-tetanic facilitation, lasting for 10 mins. The conditioning tetanic stimulation, continued for 1 min., fails to evoke a visible response. The first post-tetanic twitches are relatively feeble, but become progressively stronger until a maximum is reached in about 2 mins. after which there is a more gradual decline. The rising phase of the facilitation curve might be due either to delayed development of  $F_2$ , or to its gradual unmasking as  $I$  subsides. The latter hypothesis is supported by several observations.

First, the earliest twitches are weaker after a prolonged than after a short series of conditioning volleys. Increasing the number of the latter prolongs not only the total period of facilitation, but also the delay before the maximum is reached. Following tetani of only 1 or 2 secs., the rising phase of the facilitation curve may be so brief that the test stimuli must be timed only 1 or 2 secs. apart in order to demonstrate it at all. The rising phase is briefer, in the tibialis

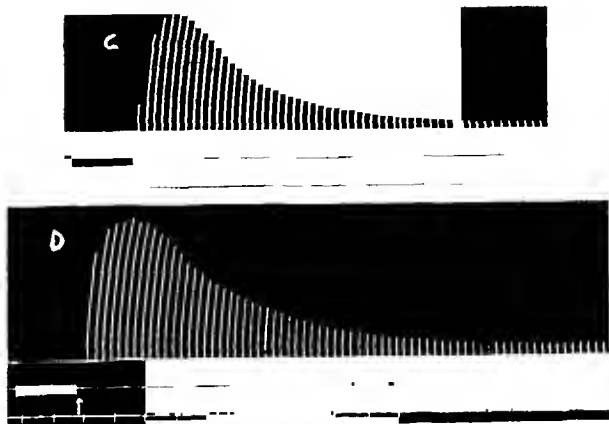


FIG 4 (continued) C and D, dog, 11.5 kg, nembutal and curare. Single shocks to nerve at 8-second intervals throughout, tetanic stimulation (Harvard coil, 1 min) at signals. At arrow (D) 3 cc. of 4 per cent KCl injected into right iliac artery.

and also in the tongue of the dog, than in corresponding muscles of the cat; but it can always be demonstrated with suitable spacing of the single test shocks.

Second, a series of post-tetanic twitches is temporarily suppressed during a second period of high-frequency stimulation. Afterward, however, the twitches reappear and become stronger. This is illustrated in Fig. 5C, the

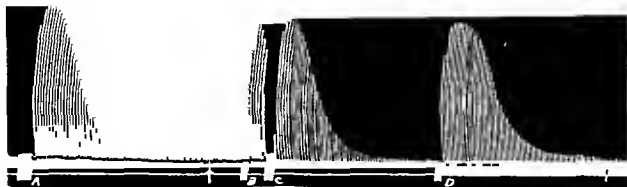


FIG 5 Dog, nembutal, curare. Single shocks at 7-second intervals applied to nerve throughout. A and C, tetanic stimulation (Harvard coil) through steel needle electrodes in muscle; B and D, tetanic stimulation through a second pair of electrodes on nerve.

suppression being due in that instance to a weak tetanic stimulation through electrodes on the muscle; but the same effect can be produced by stimulation of the nerve trunk.

Third, the post-tetanic recovery becomes briefer and less complete as the interval between test stimuli is shortened. This is shown in Fig. 6A. The op-

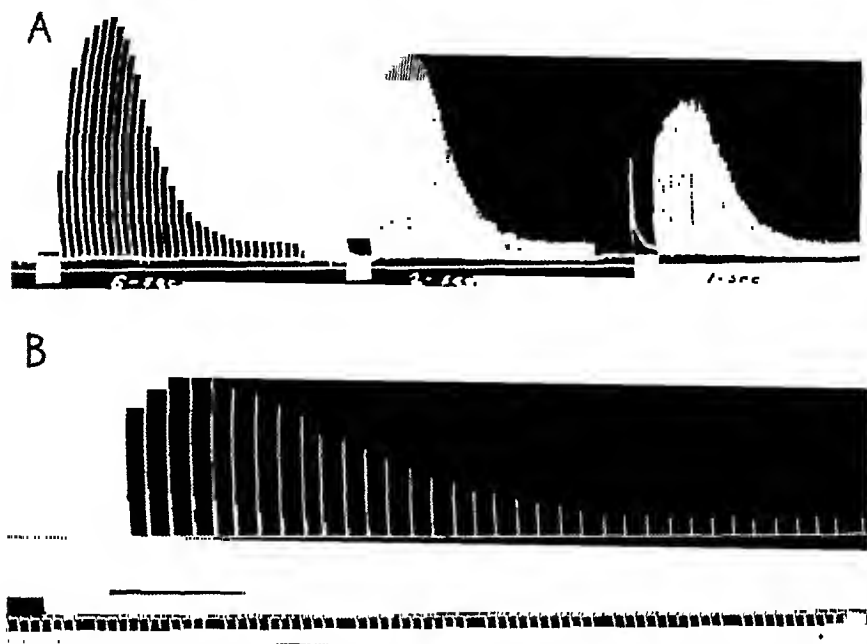


FIG. 6. A, cat, nembutal, curare. Three periods of tetanic stimulation of nerve (Harvard coil, 15 sec.) indicated by signals. Frequency of post-tetanic single shocks 10, 30, and 60 per min., in order given.

B, cat, nembutal, curare. At signal, tetanic stimulation of nerve, 100 per sec., for 30 secs. This followed by paired stimuli 1 sec. apart (interval between pairs 10 secs.) throughout remainder of record.

timum interval between single test shocks is greater than 10 secs. The response to each volley of impulses evidently is inhibited through the after-effect of the preceding volleys, unless the interval is long enough to allow the inhibitory effect to subside completely. The relation is brought out more clearly in Fig. 6B, which shows pairs of twitches 1 sec. apart with a 10 sec. interval between pairs. The second twitch of each pair is much weaker than the first. The first volley of each pair thus leaves an inhibitory after-effect which runs its course against a background of sustained facilitation. It seems certain, therefore, that  $F_2$  and  $I$  can exist together without mutual extinction, the latter dominating while it is present.

Fourth, under Mg the post-tetanic facilitation is not delayed. This is clear from the graphs shown by Lubinska (1935) and confirmed by us in (b) below. The difference between the "curare" curve and the "Mg" curve may be readily explained on the basis of an absence of masking under Mg.

We have no theory to offer concerning the identity of  $I$ , nor can we explain why it is so much more powerful and prolonged under curare than it is under Mg. In a previous paper (Maaske, Boyd and Brosnan, 1938) we questioned

the assumption of Rosenblueth and Morison (1937) that  $I$  is a reduction in size of quanta of ACh. Some other hypotheses can with more certainty be excluded.

The rising phase of the recovery curve is not due to local stimulation fatigue of the nerve, which might be expected temporarily to reduce the number of motor fibers excited. The same type of recovery curve is obtained when two pairs of electrodes are used, one for single test shocks and the other for tetanizing. The two may be placed at different levels on the nerve, or one pair on the nerve and the other on the muscle. Tetanic stimulation through electrodes on the muscle is followed by a return of the response to single shocks applied to the nerve. Under these conditions, the tetanic stimuli may be made so weak that the muscle shows only a very feeble direct response, or even none at all. Yet powerful post-tetanic twitches appear (Fig. 5A). Evidently, therefore, the intramuscular nerve fibers have a threshold lower than that of the muscle, and under the conditions described may be selectively stimulated to produce effects identical with those of stimulating the nerve trunk. Guttman, Horton, and Wilber (1937) failed to obtain post-tetanic enhancement or facilitation on direct stimulation of the curarized frog's gastrocnemius; but they also failed, as did Boyd (1932) to obtain it from stimulation of the nerve in the same preparation.

Feng (1937) describes a similar delay in the appearance of facilitation following tetanic stimulation of the nerve in a partially fatigued preparation. He

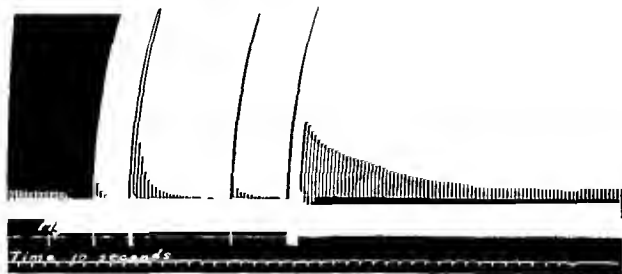


FIG. 7. Dog, nembutal and  $MgSO_4$ . Single stimuli to nerve at 4-second intervals throughout record.  $Mg$ , final dose of  $MgSO_4$ . Later signals, tetanic stimulation of nerve (Harvard coil) for 1, 3, 1, and 10 secs.

ascribes the delay to the paralytic action of an excess of ACh, and the facilitation itself to the same substance, acting after the depressing excess has been removed. It seems unlikely that ACh can remain undestroyed for so long a time after its release. In the curarized preparation, if ACh be injected into the iliac artery during the rising phase of a recovery curve, the smallest effective

dose potentiates the twitch responses instead of depressing them (Fig. 4B). KCl similarly administered also has a potentiating action (Fig. 4D). The delayed appearance of facilitation is therefore not due to the presence of a depressing excess either of ACh or of K.

(b) *Magnesium*. Under Mg the post-tetanic twitches are maximum immediately after a tetanus (Fig. 7). The decline may begin at once, or after a series of uniform maximum twitches, depending on the number of the conditioning volleys. The post-tetanic recovery and the secondary component of the tetanus itself (see section 1, b, above) are evidently made possible by the same facilitating factor, reaching its maximum development during the tetanus and persisting for some time afterward. With increasing dosage of Mg, a stage is reached at which no post-tetanic recovery is demonstrable; but at this time a feeble, delayed contraction still appears *during* high-frequency stimulation of the nerve. As pointed out above, the effects under curare disappear in the reverse order. Post-tetanic facilitation, under Mg, is not suppressed by a second period of high-frequency stimulation of the nerve; nor is its course appreciably affected by changes in the frequency of the single test shocks.

### SUMMARY

1. During neuromuscular depression, produced in the mammal either by curare or by Mg, tetanic stimulation of a motor nerve results in junctional facilitation. This appears in two phases. The first is the latent addition studied by Bremer and Homès (1932). The second, much more prolonged, has been described by Boyd (1932, curare) and by Lubinska (1935, Mg).

2. Under curare, the two phases are entirely separated in time by a period of Wedensky inhibition. During this period a facilitating factor is present, but is masked by the inhibitory factor. The two can coexist without mutual extinction.

3. The inhibitory factor is not a depressing excess of acetylcholin nor of potassium; nor is it a local change affecting the nerve at the site of stimulation. It is far more powerful under curare than under Mg.

4. Under Mg, the two phases of facilitation overlap in time. The only evidence of discontinuity is a partial and transient relaxation which appears shortly after the beginning of a tetanus.

5. Demonstration of the masking effect mentioned in (2) supports the hypothesis of Brown and von Euler (1938) that both phases of facilitation are due to a single factor. It is not yet certain, however, that the separation between the two phases is entirely due to masking.

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## A FURTHER STUDY OF THE CROSSED PHRENIC PHENOMENON

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SCHIFF (1894) and Porter (1895) showed that severance of a phrenic nerve in dogs or rabbits results in respiratory contractions of the contralateral hemidiaphragm paralyzed by a spinal semisection on the same side at or above C3. In a previous publication from this laboratory (Rosenblueth and Ortiz, 1936) control experiments on the Schiff-Porter crossed phrenic phenomenon were reported, which led to the conclusion that the appearance of the crossed diaphragmatic contractions upon section of the active phrenic is not due to relative asphyxia or to changes in the afferent nerve impulses set up by the respiratory movements, but that the direct cause of the phenomenon is the severance of the motor fibers in the phrenic. This conclusion entailed the postulation of properties of nerve cells different from that of conducting nerve impulses and unparalleled in any other known experimental conditions. The present study was undertaken to obtain further controls which would support or invalidate this conclusion and its unexpected corollaries.

### METHODS

Rabbits and cats were employed. The acute experiments were usually performed under dial anesthesia (Ciba, 0.55 to 0.6 and 0.6 to 0.75 cc. per kg., respectively, intraperitoneally). In some of the rabbits intravenous urethane supplemented the dial; in a few instances urethane alone was given. In the early experiments the diaphragmatic contractions were recorded as described by Rosenblueth and Ortiz, by attaching serrefines connected to recording levers via threads and pulleys to the two diaphragmatic domes just lateral to the tendinous center, after opening the abdomen. Contractions of the diaphragm appear in such records as downward excursions of the kymographic tracing.

In later experiments it was found that Head's slips, which attach to the xyphoid cartilage in the rabbit, provide a more accurate and simpler index of diaphragmatic activity. A midline section of the xyphoid cartilage was made. The muscle was separated from the bony part of the xyphoid process and this bone was cut. Quite independent tracings of the activity of each half of the diaphragm were obtained by attaching the serrefines to the freed fragments of cartilage. In cats, although Head's slips are not as developed as in the rabbit, a similar preparation yielded equally satisfactory results. In the records obtained by this procedure diaphragmatic contraction is denoted by upward excursions of the tracing. For the application of reversible ether blocks the sterno-mastoid muscle was cut at its lower insertion, thus permitting a clear exposure of the phrenic nerve down to C7. A small piece of cotton soaked with ether was then placed on the nerve and removed as soon as the block was complete.

Alternating or direct current was applied to the phrenic for blocking purposes by means of shielded silver electrodes placed between C6 and C7. The component to the phrenic from C7 was eliminated by cutting this nerve at its emergence from the vertebral column—i.e., centrally to the phrenic. The alternating current used was faradic induction shocks from a Harvard coil with 5 volts in the primary circuit. Direct current was obtained from a battery, the intensity being regulated by a potentiometer and measured by a voltmeter. Afferent stimulation of the median, the vagus or the saphenous nerves was faradic, through shielded silver electrodes, after cutting the nerves peripherally. Asphyxia was produced either by attaching to the tracheal cannula a rubber balloon containing nitrogen or expired air, or by occluding the cannula.

The operations which were carried out on some of the animals previous to the acute experiments were made aseptically under ether anesthesia. Other details of the methods employed in particular instances will be found in the corresponding sections below.

### RESULTS

*Animals with a previously cut phrenic nerve.* The purpose of these experiments was two-fold: first, to see whether crossed contractions would appear when the spinal semisection was performed several weeks after cutting the phrenic; and second, to investigate the influence upon the phenomenon of the functional connection of the cut nerve with some structure other than the diaphragm. Accordingly, in 19 rabbits and 9 cats, one phrenic nerve was cut below C7 and its connection with that nerve was severed. The freed central end of the phrenic was then sutured either to the peripheral end of the cut cervical sympathetic, or, more frequently, to the sterno-mastoid muscle, denervated by section of the spinal accessory nerve. One to 25 weeks later the animals were anesthetized with dial, a spinal semisection at C2 contralateral to the previous section of the phrenic was performed, the abdomen was opened and the diaphragm was either observed directly or, more commonly, hooked up for recording in the usual manner. The effects of section of the previously cut phrenic and of the vagi were studied. Regrowth, when present, could be detected by activity in either the pupil or the sterno-mastoid, coincident with the respiration.

The results are summarized in Tables 1 and 2. In the columns marked *Re-*

Table 1  
Operated Rabbits

Animal No	Time after operation (weeks)	Regrowth	Results of semisection	Results of cutting phrenic	Results of cutting vagi
1	1	0	++		
2	2	0	++		
3	4	0	++		
4	4	0	++		
5	5	0	++		
6	6	0	++		
7	13	0	0	0	++
8	22	0	++		+
9	24	0	++		
10	13	+	0	0	+
11	13	+	0	0	0
12	13	+	+	+	+
13	24	++	+		
14	13	+++	+		++
15	13	+++	0	0	0
16	20	+++	+	SI +	++
17	24	+++	++	0	++
18	24	+++	0	++	++
19	24	+++	0	0	0

\* The section of the regrown phrenic followed section of the vagi

\*\* The section of the phrenic was incomplete, later completion led to no further change

Table 2  
Operated Cats

Animal no.	Time after operation (weeks)	Regrowth	Results of spinal semi-section	Results of cutting phrenic	Results of cutting vagi
1	25	0	+	+	+
2	23	0	0	0	+
3	23	0	++		
4	16	0	+++		
5	23	+	0	0	+
6	20	+	++	++?	++
7	19	+	+++		
8	18	++	+	0	
9	16	++	0	0	+

*growth*, O stands for no detectable functional connections of the anastomosed phrenic; the + signs indicate slight, medium or marked functional regrowth. In the columns marked *Results of semisection* the + signs denote crossed contractions of the diaphragm immediately after semisection—i.e., the hemidiaphragm on the side of the semisection did not stop breathing; O stands for complete paralysis of the diaphragm. The columns marked *Results of cutting phrenic*, or *vagi*, indicate the changes in the magnitude of the contractions of the crossed hemidiaphragm—i.e., of the side ipsilateral to the cord semisection, with intact phrenic—upon section of the anastomosed phrenic or the vagi. The sign O stands for no detectable change and the + signs denote either the appearance of crossed contractions, if the diaphragm was previously paralyzed, or the increase of pre-existing crossed contractions.

The following results deserve emphasis. (a) With two exceptions (rabbit 7 and cat 2) in the animals in which there was no regrowth, spinal semisection elicited prompt marked crossed contractions. (b) In 7 out of the 15 animals with regrowth, spinal semisection did not elicit crossed contractions; in 4 of these animals a crossing occurred later. (c) Up to 24 weeks after cutting the phrenic, spinal semisection may lead to immediate crossing (rabbit 9, cat 1). (d) Immediate marked crossed contractions may appear upon spinal semisection even when good functional regrowth of the cut phrenic has taken place (rabbit 17, cats 7 and 8). (e) Section of the regrown phrenic (incomplete, rabbit 18) may lead to crossing. (f) Section of the vagi may cause crossing after the phrenic has been cut, even though there has been no obvious regrowth (rabbit 7, cat 2), or when such regrowth is present (rabbit 10, cats 5 and 9).

*Direct electrical stimulation of the respiratory center or the respiratory tract above C3.* Five cats were tested. The results were clear and consistent. Recording from the diaphragmatic domes or from Head's slips was attempted, but the passive movements of the diaphragm transmitted via the chest from contractions of the neck muscles were as a rule confusingly prominent. Visual observation of the diaphragm after wide opening of the abdomen was, therefore, more satisfactory.

The following protocol is typical of the procedure followed and the results obtained. Cat, anesthetized with dial (0.65 cc. per kg. intraperitoneally). Tracheal cannula inserted. Vagi, cervical sympathetics and depressors cut in the neck. Carotids ligated and spinal accessories cut. Cervical nerves C3 to C7 cut peripherally to the phrenics, on both sides. Complete transection of the spinal cord immediately below C7. Left semisection of the cord at C3. Animal breathing only with its right diaphragm; artificial respiration now applied. Cerebellum removed. Midline longitudinal section of the medulla and cord from the upper part of the 4th ventricle to C2. Left semisections at the upper and lower limits of this midline incision and removal of the segment isolated by these sections. Slight compression of the vertebral arteries throughout these procedures to control hemorrhage, when necessary.

Stimulation of either the right respiratory center (electrodes applied to the medial surface of the sectioned medulla just above the tip of the calamus scriptorius; coil distance about 10 cm.) or of the right respiratory tract (electrodes applied to the lateral surface of the cord at C1 or C2; coil distance about 8 cm.) caused marked contractions of the right hemidiaphragm with no involvement of the left side. The right phrenic nerve was then cut. Similar stimulation elicited now strong contractions of the left hemidiaphragm; the right side was of course paralyzed. Completion of the semisection of the cord at C3—i.e., complete transection at that level—abolished the diaphragmatic responses, thus proving that the contractions of the left hemidiaphragm had not been elicited by spread of the stimuli to the left respiratory tract below C3.

*Reversible alternating-current or direct-current blocks.* Rosenblueth and Ortiz (1936) showed that reversible blocks of the active phrenic after a high spinal semisection, produced by applications either of direct current or of ether, resulted in respiratory movements of the previously paralyzed hemidiaphragm. These crossed contractions appeared only when all the motor fibers in the active phrenic were blocked but did not subside until after complete recovery



FIG. 1. Rabbit; dial. Left spinal semisection at C2. Electrodes on intact right phrenic below C6; C7 cut centrally to the phrenic. Records from Head's slips; upper: left; lower: right. In this and the succeeding figures the time signal registers 5-second intervals.

A. Faradic stimulation of the right phrenic. Coil distance: 12 cm. and 60° angle.  
B. Tracheal cannula occluded for the same time.

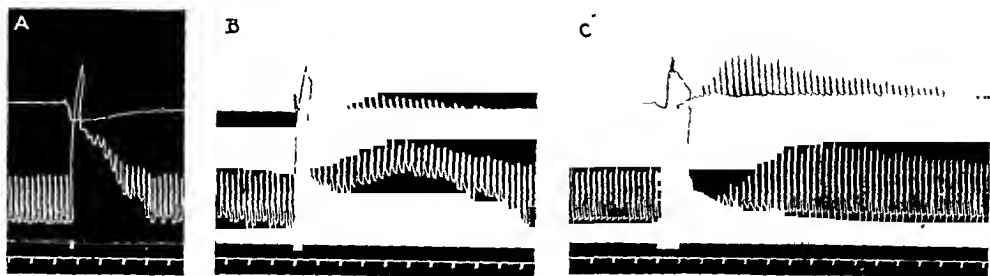


FIG. 2. Same preparation and records as in Fig. 1. Faradic shocks delivered to the right phrenic; coil distance 8 cm. A: 1 sec. B: 2 secs. C: 5 secs.

of the blocked phrenic. In the phase of subsidence, therefore, both hemidiaphragms, direct and crossed, contracted simultaneously for some time.

The purpose of the present observations was to study the influence of various intensities and durations of the reversible blocks on the delay, magnitude and time-course of the crossed effects. For this reason alternating and direct current were used since they can be accurately gauged as blocking agents, and were preferable to ether. In general it may be stated that as the blocking currents are intensified or applied for longer periods, thus increasing the block, the crossed effects come earlier and are bigger and more prolonged. If very weak A.C. or D.C. currents are used, which do not lead to blocking of the motor nerve fibers even when applied for long periods (up to 1 min.), no crossed contractions appear as a rule. When they do occur they are delayed and small, and are probably due to relative asphyxia of the animal (see next section) because of the prolonged tetanic contraction of the active hemidiaphragm.

Stronger currents, capable of producing complete block, if applied for a few seconds, result in crossed contractions. The longer the duration of the block,

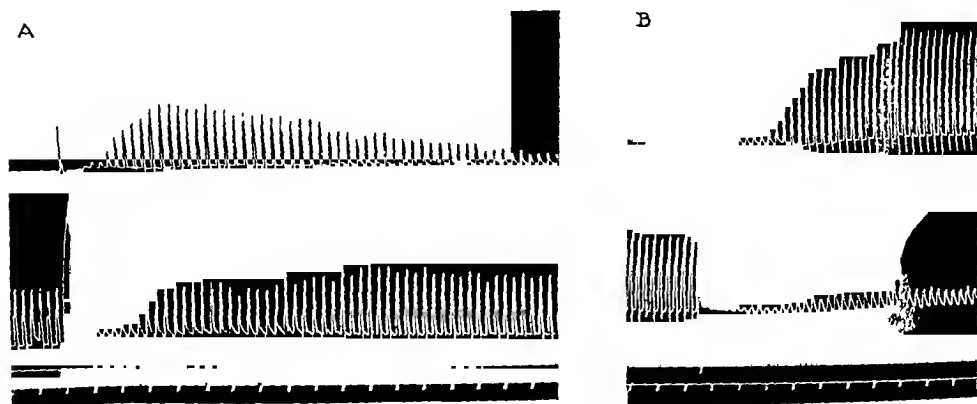


FIG. 3. Same preparation and records as in Figs. 1 and 2.

A. Faradic shocks delivered to the right phrenic for 1 sec.; coil distance: 7 cm.  
B. At signal section of the right phrenic.

the more prolonged the crossed effects. Blocks of similar duration can be produced by currents of different intensity by adjusting the periods of application. Thus, a brief strong current may result in a complete block of the same duration as that produced by a weaker current applied for a longer period. In such cases there is a tendency for the stronger current to elicit more marked crossed effects—*i.e.*, stronger and more prolonged—than those brought out by the weaker current. Figs. 1, 2 and 3 illustrate some of the points mentioned. In Fig. 1 it is shown that the small delayed crossed contractions elicited by

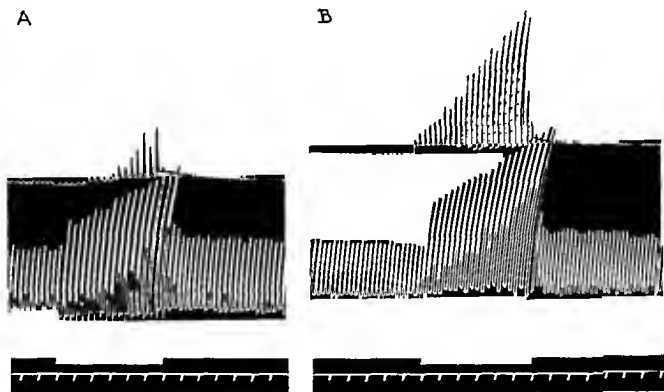


FIG. 4. Effects of asphyxia before and after reversible crossing. Cat; dial. Left spinal semisection at C2. Right C7 cut. Head's slips; upper record left, and lower record right hemidiaphragm. At signal, tracheal cannula occluded.

A. Before any reversible crossing.

B. After three reversible crossings from the application of A.C. to the right phrenic below C6.

prolonged non-blocking stimulation of the active phrenic closely resemble the contractions evoked by a similar period of asphyxia. In Fig. 2 the increasing effect of increasing duration of the blocking A.C. is demonstrated. In Fig. 3 the similarity in the onset of the crossed contraction elicited by a strong block and by cutting the phrenic is emphasized.

*Respiratory reflexes and asphyxia.* The purpose of these observations was to compare the effects of increased respiratory discharges on the hemidiaphragm paralyzed by a high spinal semisection, before and after the application of a reversible block to the active phrenic. The experimental procedure consisted in making a left spinal semisection at C2 and applying stimulating electrodes on several afferent nerves and sometimes also on the active right phrenic. The results of stimulating the afferent nerves and of asphyxia were

then observed and recorded from the two hemidiaphragms. After these preliminary records were obtained, one or more reversible ether or electrical (A.C. or D.C.) blocks were applied to the right phrenic. These blocks resulted in a transient appearance of respiratory contractions of the left, previously paralyzed hemidiaphragm. The afferent nerves were then again stimulated and asphyxia produced, as before the reversible crossings.

Rosenblueth and Ortiz (1936) reported that asphyxia did not lead to any crossed contractions unless it was applied after a reversible crossing had been obtained by a transient block of the active phrenic. In the present observations, in some animals (rabbits and cats) a crossing was observed during

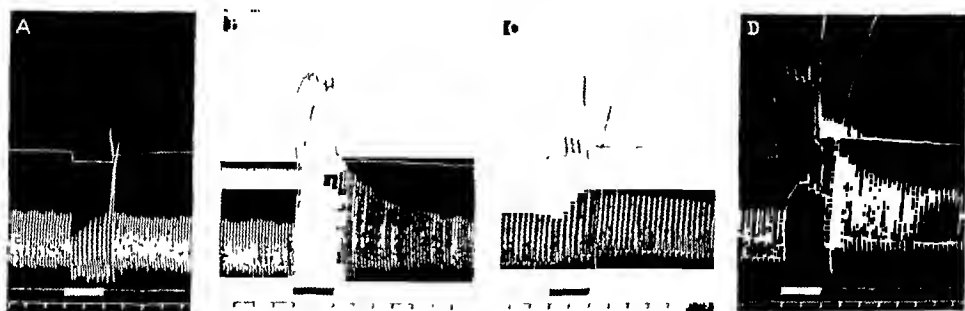


FIG. 5. Appearance of crossed reflex contractions after reversible crossing. Rabbit; dial. Left spinal semisection at C2. Right C7 cut. Head's slips; upper record: left, and lower: right. A and B, before any crossing had occurred. C and D, after two reversible crossings from the application of A.C. to the right phrenic below C6. A and C: afferent stimulation of the right median nerve (coil distance 8 cm.). B and D: afferent stimulation of the left vagus (coil distance 8 cm.).

asphyxia in the preliminary control records. Such crossing did not occur, however, until the asphyxia was pronounced, and subsided promptly upon cessation of the asphyxiating procedure (Fig. 4A). Production of a similar degree of asphyxia after one or more reversible crossings elicited prompt, vigorous crossed contractions, which did not cease immediately when the animal was allowed to breathe freely (Fig. 4B). The results of afferent stimulation in rabbits were similar to those of asphyxia. Crossed contractions occurred in some animals before any reversible blocks had been applied to the active phrenic. Such reflex crossed contractions were, however, as a rule delayed and weak, and subsided promptly after cessation of the stimuli. After one or more reversible crossings, on the other hand, the reflex effects were more prompt, vigorous and enduring than before. Fig. 5 illustrates a typical instance.

*Effects of cutting the vagi.* Section of the vagi in normal rabbits results in respiratory changes similar to those found in cats and dogs—i.e., the respiration becomes slower and deeper. In rabbits with a high spinal semisection in which the vagi are cut before any crossed diaphragmatic contractions have been produced by blocking or cutting the active phrenic, the results of cutting the vagi are the same. In the rabbits in which the vagi were cut after the active phrenic had been severed, or only reversibly blocked, the change of the

respiratory frequency consisted usually in an acceleration (Fig. 6). Similarly, in the operated rabbits reported in section A, cutting the vagi produced a respiratory acceleration. These results are summarized in Table 3. In the cats, whether the vagi were cut before or after crossing, the effect was usually a slowing of the respiration.

Another consequence of severing the vagi is the following. In animals, cats or rabbits, in which no reversible crossed effects had been elicited, such a section did not result in crossed contractions. But if one or more reversible blocks, with the corresponding transient crossings, had been applied, then sec-

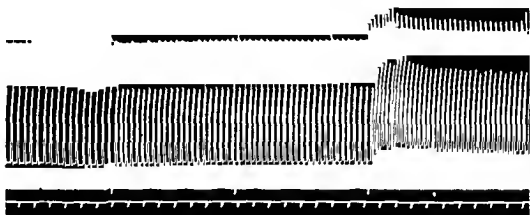


FIG. 6. Rabbit; dial. Left spinal semisection at C2. Head's slips; upper: left; lower: right. Before this record was taken 4 reversible crossings had been produced by application of D.C. to the right phrenic. At signals: first, section of right vagus; next, section of right cervical sympathetic; last, section of left vagus.

tion of the vagi frequently led to the immediate appearance of crossed contractions, which subsided slowly. Fig. 6 illustrates a typical instance. It may be recalled that in the operated animals section of the vagi led also in several cases to the appearance of crossed contractions (Tables 1 and 2).

*Changes of rate during crossing.* In the rabbits, whether the crossing was transient, by applying a reversible block to the active phrenic, or permanent, by cutting the nerve, the respiratory rate was usually slower during the period of crossed contractions than before the crossing. This slowing was observed in various experimental conditions summarized in Table 4. Figure 7 illustrates typical instances. In the cats the changes of rate during crossing were less marked than in the rabbits. They consisted usually in a slowing followed by recovery of the normal rate, although the crossed contractions persisted.

## DISCUSSION

Rosenblueth and Ortiz (1936) reported that in some cats a high spinal semisection did not lead to an ipsilateral respiratory hemiplegia. In the present experiments a respiratory hemiplegia was absent only when the spinal semisection was incomplete. In the rabbit, as Porter (1895) pointed out, all the nerve fibers descending from the respiratory center to the spinal motoneu-



rons travel superficially in the external region of the lateral columns. Even a small section of the cord in this region, not reaching the nerve fibers in the neighborhood of the midline, will, therefore, usually result in an ipsilateral respiratory paralysis. In the cat, on the other hand, there probably are some descending respiratory fibers placed medially, besides the lateral tract analogous to that in the rabbit. For this reason an incomplete semisection will fail to paralyze entirely the corresponding respiratory muscles. Once this condition was recognized the spinal sections in cats were made to overlap the midline and invariably resulted in the desired hemiplegia. Indeed, cats may be more satisfactory than rabbits for the study of the phenomenon, in as much as crossed contractions upon blocking or cutting the active phrenic have occurred

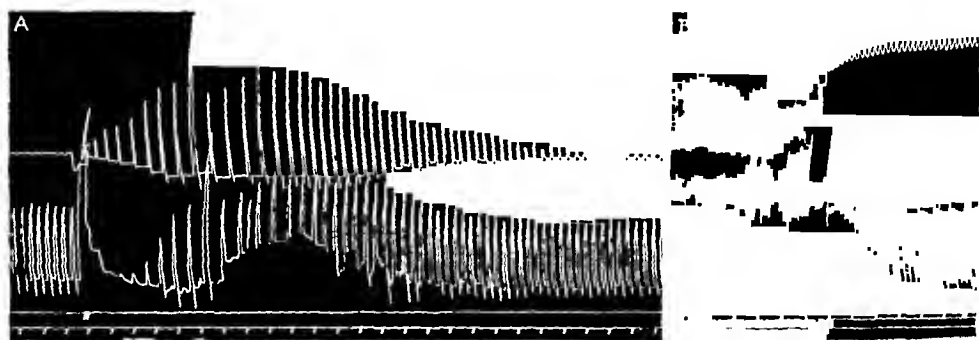


FIG. 7. Slowing of the respiration during crossed contractions.

A. Rabbit; dial. Left spinal semisection at C2 and complete transection at C7. Head's slips; upper: left; lower: right. At signal A.C. (coil distance 8 cm.) applied for 1, sec. to right phrenic below C6.

B. Rabbit; dial. Left spinal semisection at C2. Vagi, cervical sympathetics and depressors cut. Records from the diaphragmatic domes; upper: right, lower: left. At signal, right phrenic cut.

in all the cats tested, whereas occasionally the crossed contractions have entirely failed to appear in some rabbits. Rosenblueth and Ortiz (1936) reported 4 rabbits in which no crossing took place. These 4 animals had had a bilateral section of the vagi, cervical sympathetics and depressors, before the active phrenic was blocked or cut. It was thought that the previous operations were responsible for the absence of the crossed contractions.

This inference was invalidated in the present series of rabbits by 4 animals in which a prompt typical crossing occurred upon cutting the active phrenic after cranial nerves IX, X, XI and XII and the cervical sympathetic trunks had been cut. Other instances of lack of crossing in rabbits were again encountered here, and no correlation could be established with the experimental procedures, the strains of rabbits used, the anesthetic employed or the depth of anesthesia. Unless the animals are grossly over-anesthetized, crossing may occur under ether, dial, dial with additional urethane, urethane alone or chloralose. In the total number of normal rabbits (*i.e.*, unoperated previously) used thus far in this Laboratory for the study of the phenomenon, there have

been 10 instances of negative results—i.e., no crossing on cutting the active phrenic, or by any other procedure—as opposed to 50 positive instances. These figures are of importance in judging the results obtained in the operated animals.

It is significant that 3 out of the 9 cats and 6 out of the 19 rabbits in which a phrenic had been previously cut did not present an immediate crossing upon performing a contralateral high spinal semisection (Tables 1 and 2). That the absence of crossing in such conditions is probably correlated with the functional regrowth of the cut nerves into the structures to which they had been anastomosed is indicated by the fact that with the exception of only 2 animals an immediate crossing occurred whenever there was no evidence of regrowth. Indeed, it is possible that in the exceptional animals a slight regrowth was present but not detected. If the appearance of the crossed contractions were due to either relative asphyxia or to quantitative changes in the number and distribution of afferent impulses set up by the respiratory movements, an immediate crossing would have taken place in all the operated animals upon performing the high spinal semisection, regardless of whether the cut phrenics had regrown into other structures or whether such regrowth had not occurred. Since this was not the case, however, the evidence from the operated animals supports the conclusion previously reached (Rosenblueth and Ortiz, 1936) that the crossing is not primarily due to either asphyxia or changes in afferent bombardment of the centers.

The evidence obtained by electrical stimulation of the respiratory center or the respiratory tract supports this conclusion more directly. The number of nerve impulses delivered to the phrenic motoneurons was probably constant, since the stimulus was not varied. Complete paralysis of the respiratory muscles except during stimulation and uniform artificial respiration eliminated any significant changes in afferent bombardment. Yet crossed contractions only appeared after the phrenic on the direct side was cut. The inference again emerges that the crossing is due to section of the motor axons in the phrenic. Such a section is followed by changes in the phrenic motoneurons or related internuncials in the spinal cord, so that the descending respiratory impulses then become able to activate liminally the contralateral phrenic motoneurons.

The experiments on the effects of A.C. or D.C. blocks of different intensities and durations (Figs. 1, 2 and 3) are in agreement with the previous conclusions. When the current applied to the active phrenic is not sufficiently strong to block all the motor fibers, no crossing occurs. This is in keeping with the similar facts reported by Rosenblueth and Ortiz (1936) when ether blocks were employed, or when the phrenic was cut in stages by sectioning the cervical nerves progressively. If asphyxia or changes in afferent nerve impulses played a major part in the phenomenon, the crossing should take place even when only some of the motor fibers are inactivated and should be approximately proportional to the number of fibers blocked. Such is not the case.

The crossed effects are, on the other hand, a function of the magnitude

(intensity and duration) of the block produced, since they are more prompt, greater and more prolonged, the deeper and longer the block of all the motor fibers (Fig. 2). Notwithstanding this proportionality the records reveal an independence of the time course of the block on the direct side and the respiratory contractions on the crossed side. Depending upon the intensity and duration of the blocking currents applied, the subsidence of the crossed effects may be rapid and begin while only a few of the blocked motor fibers have recovered, or it may be slow and begin after all the motor fibers on the direct side have recovered from the block. It may therefore be concluded that the central effects of the block are a function of its magnitude, but are independent of the changes in the respiratory movements which the block elicits.

The observations (Figs. 4 and 5) also support the conclusion that once the crossed path has been opened by a reversible block subsequent crossings are more readily obtained and more pronounced (Rosenblueth and Ortiz, 1936). When the effects of the reversible block have subsided, although the original condition seems reestablished, the centers have really different properties in this respect, at least as long as the experiment lasts. This central change takes place probably at the spinal cord, since the discharges of the respiratory center during asphyxia or the reflexes, as judged by the contractions of the direct side, are no greater after the block than before its application.

In dogs, section of the vagi leads usually to the permanent appearance of crossed discharges (Rosenblueth and Ortiz, 1936). In normal—*i.e.*, not previously crossed—rabbits or cats, section of the vagi has never been observed to result in crossed contractions. On the other hand, the influence of the vagi on the crossed phenomenon is apparent in the animals in which the section is made after a crossing has taken place (Fig. 6; Tables 1 and 2). The difference between the dogs and cats or rabbits may therefore be only quantitative in this regard. With the data available, the problems of the mechanism, site and nature of the central changes produced by section or blocking of the phrenic are open only to speculation. The present observations offer, however, some clues worthy of consideration. As shown above (pp. 510, 514) the experiments suggest that some of the changes take place in the spinal cord—phrenic motoneurons or possible internuncial neurons—as opposed to the medullary cells of the respiratory center. Such evidence might be explained by postulating changes in only the cut or blocked neurons.

The data in Figs. 6 and 7 (See Tables 3 and 4), suggest on the other hand, that the effects of section or block transcend the neurons directly affected. Changes of rate which involve not only the diaphragm, but also all other respiratory muscles, are to be attributed to modifications taking place in the respiratory center.

It thus appears likely that the local changes in motor fibers to which electric currents are applied for a brief period have a widespread influence on the properties of central neuron systems. The propagation occurs by some mechanism different from that by which nerve impulses are conveyed. The changes are probably not unineuronal, but extend beyond the synaptic confines.

Table 3

Changes in respiratory rate upon cutting the vagi in rabbits. The figures indicate the number of animals in which the corresponding phenomenon was observed.

	Acceleration	No change	Slowing
<i>Normal rabbits</i>			
Before any crossing	3	5	17
After one or more reversible crossings	7	1	1
After cutting the active (direct) phrenic	2	0	0
<i>Operated rabbits</i>	14	3	0

Table 4

Changes in respiratory rate during crossing in rabbits. The figures indicate the number of animals in which the corresponding phenomenon was observed.

	Acceleration	No change	Slowing
Phrenic cut Vagi intact	0	0	5
Phrenic cut Vagi cut	2	1	7
Ether blocks Vagi intact	0	3	5
Ether blocks Vagi cut	2	1	3
A C blocks Vagi intact	0	0	2
A C. blocks Vagi cut	0	1	2

## SUMMARY

The appearance of crossed diaphragmatic contractions—i.e., ipsilateral to a spinal semisection at C2 or C3—was studied in rabbits and cats in the following experimental conditions: (i) animals in which the phrenic nerve contralateral to the spinal semisection had been cut and anastomosed either to the cervical sympathetic or the denervated sternomastoid muscle 1 to 25 weeks previously (Tables 1 and 2); (ii) animals in which the respiratory center or the respiratory tract above C3 was stimulated electrically; (iii) animals in which the active phrenic on the side contralateral to the spinal semisection was blocked reversibly by alternating or direct currents of various intensities and durations (Figs. 1, 2 and 3); (iv) during activation of the respiratory center either reflexly or by asphyxia, before and after application of reversible blocks to the active phrenic (Figs. 4 and 5).

The effects of cutting the vagi before or after reversible diaphragmatic crossings are described (Table 3, Fig. 6). The changes of respiratory rate during crossings are reported (Table 4, Fig. 7). In the discussion it is shown that the following conclusions are confirmed: (i) crossed contractions occur directly as a result of cutting or blocking the motor fibers, not as an indirect effect from relative asphyxia or from changes in the afferent impulses set up by respiratory movements; (ii) the central changes are mediated by some process which does not require the conduction of nerve impulses; (iii) once the crossed path has been opened—i.e., after a reversible block—subsequent crossings are more

readily obtained. The facts reported also suggest that some of the central changes responsible for the crossing occur at the spinal cord (pp. 510, 514). Other data (p. 513) show that in addition to these lower spinal changes there are probably also modifications in the respiratory center in the medulla, caused by the block or cut of the phrenic which leads to crossing.

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# A FOURIER TRANSFORM OF THE ELECTROENCEPHALOGRAM\*

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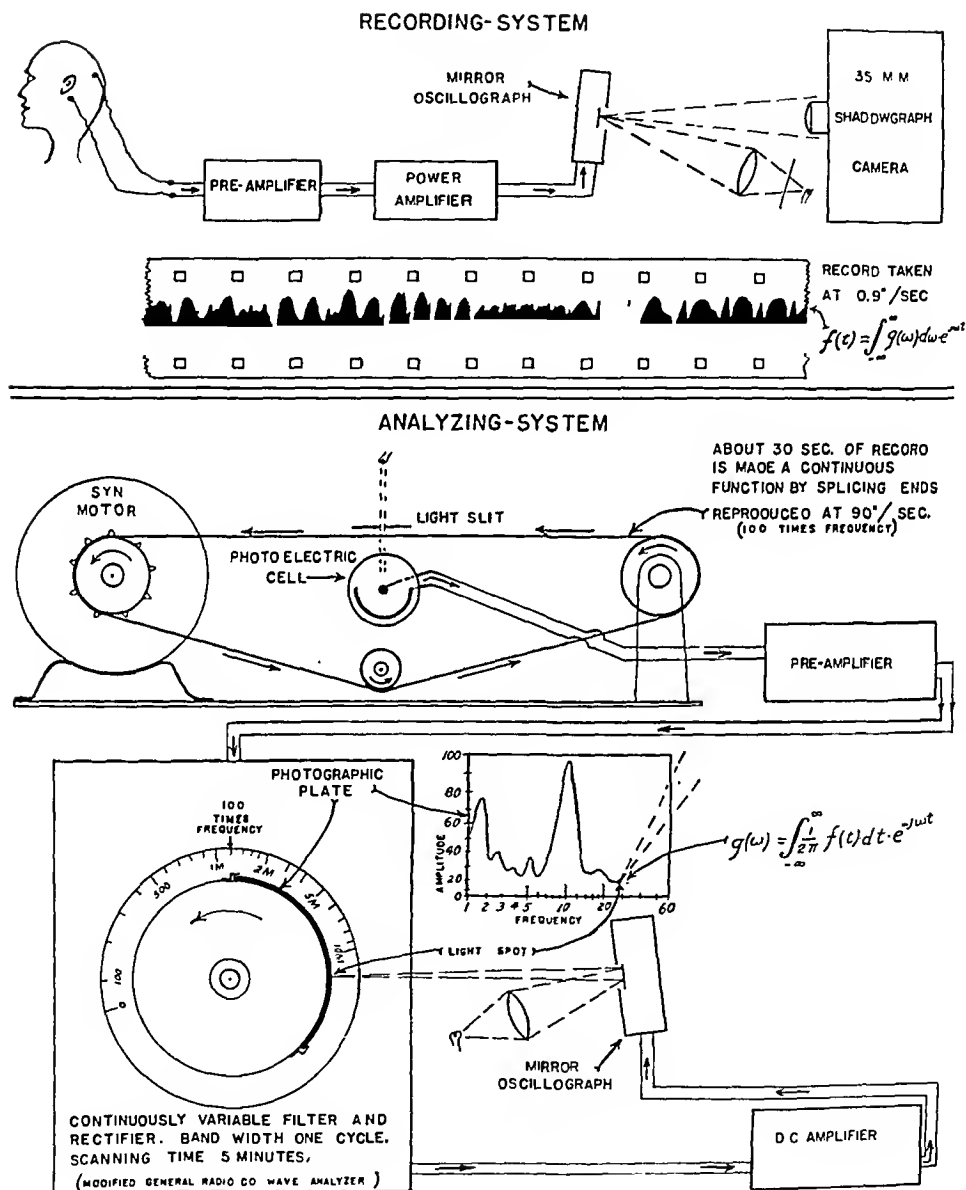
THE electroencephalogram as usually recorded shows a confusion of wave forms and a mixture of frequencies which are impossible of accurate visual analysis. With experience one can learn to detect certain gross features which have significant clinical and physiological correlates, but in this there is more art than science. Certain crude indices which have been devised as a basis for comparison are open to theoretical criticism. They are not arrived at objectively, and do not afford a consistent expression for the data. The electroencephalogram, which is an amplitude *vs.* time function, can be expressed as a continuous plot of amplitude *vs.* frequency; that is, as a spectrum. The mathematical tool for making such a transposition is the Fourier Transform. The validity of its application to the electroencephalogram in terms of its

The only question that can be reasonably argued is whether such an expression is advantageous. We believe that it is, and have applied the Fourier Transform to a large number of electroencephalograms. The theoretical and practical advantages of this expression will be set forth below.

Not the least of its advantages is the simplicity with which it can be obtained by the mechanical-electrical integrator which one of us (A.M.G.) has designed. The technique is as follows: A representative oscillogram is taken as a shadowgraph on 35 mm. film, and later made into a continuous function by splicing the film to form an endless belt. The belt is revolved between a transverse slit of light and a photo-electric cell which reproduces the original electroencephalogram (Fig. 1). The resulting signal is passed through an extremely sharp variable electric wave filter. The speed of the belt and the speed of the frequency scanning mechanism is so arranged that the electroencephalogram to be analyzed can be treated as a repetitive function in this system. After being rectified the output of the filter is connected to a galvanometer which automatically records the amplitude of each differential frequency component on sensitized coördinate paper.

No objective method of analyzing the intricate wave forms of the electroencephalogram has previously been devised. The advantage of such a method in practice is that it is independent of the several intricate and arbitrary terminologies which have been devised for compiling results of studies on the electrical activity of the brain. It affords a relatively complete yet comprehensive expression for the data in terms of itself alone. It provides a common, rigorous, and mathematical expression for all types of record. Furthermore it ends the tedious work of measuring frequency by hand, and of estimating for

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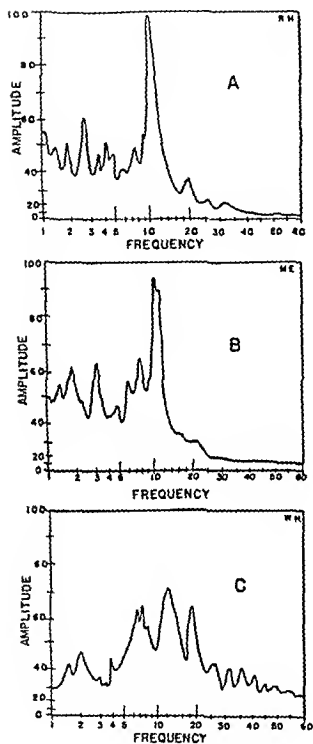


FIG. 2  
3 NORMALS

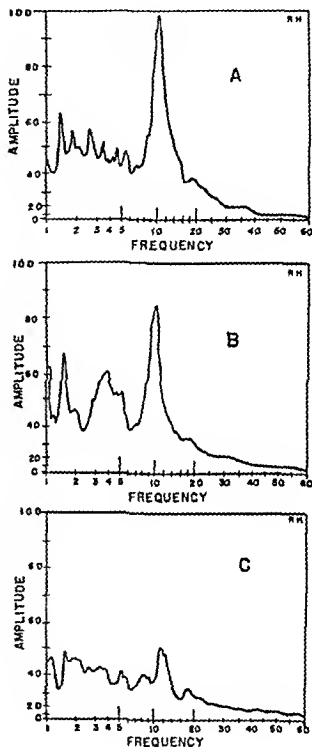


FIG. 3  
A-NORMAL, EYES CLOSED  
B-EYES OPEN, INACTIVE  
C-EYES OPEN, READING



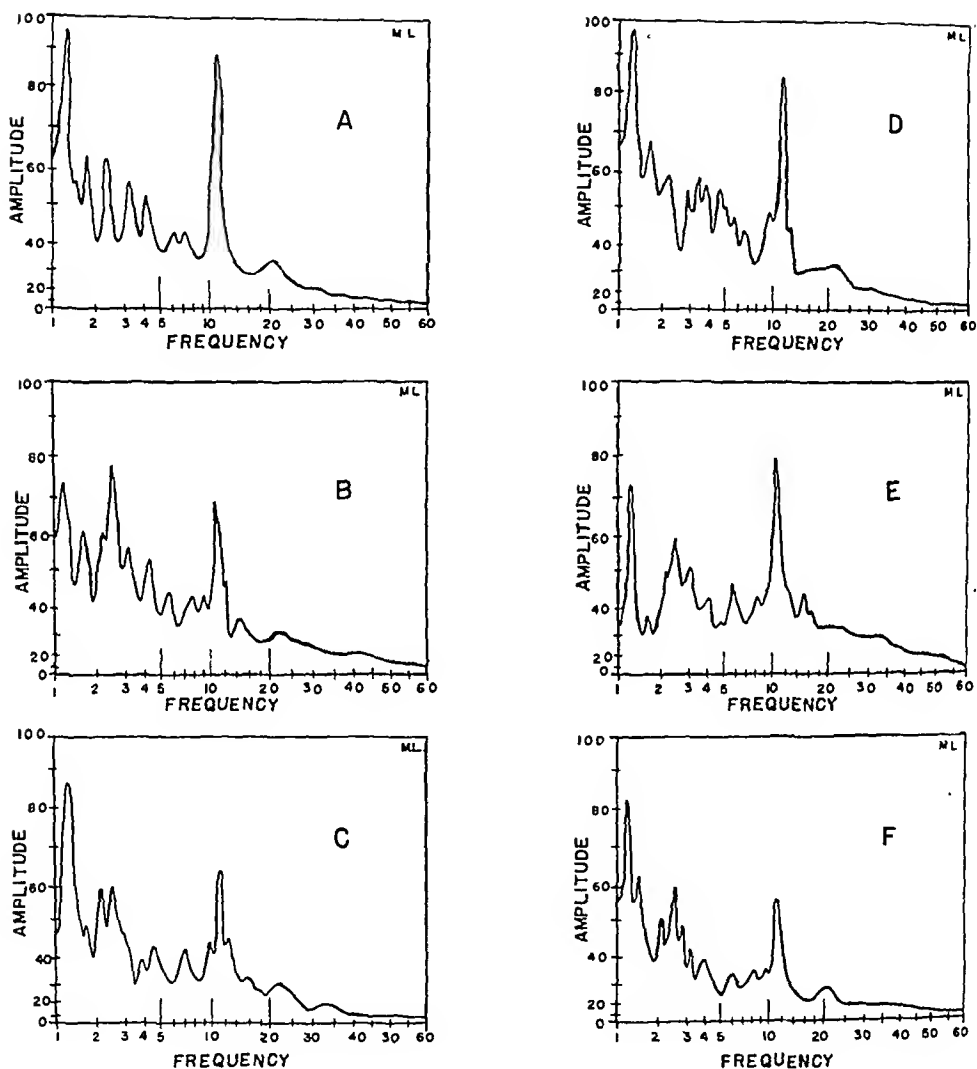


FIG. 4

ANALYSES OF RECORDS OF A NORMAL TAKEN AT 10 MINUTE INTERVALS

each component the percentage of time present, both of which procedures are as exhausting as they are inadequate and inaccurate.

The Fourier Transform is not proposed as a substitute for the customary oscillographic recording of the electroencephalogram, but rather as a supplement and a compact expression for such a record. The unanalyzed record is still indispensable for detecting short bursts of particular wave forms, phase relations, and "build-ups," all of which have been shown to be significant. These tend to be lost in the analyzed record. Nevertheless, the time element can be supplied in the form of consecutive analyses made at separate or continuous intervals of time.

Analyses have thus far been made of more than 300 records. These include a control group of 111 normals, 104 schizophrenics, and 84 epileptics. In many of the subjects observations were repeated at different intervals of time. In all cases records were taken from frontal, occipital, parietal and temporal lobes. Comparisons and data for these cases is being worked up and will be published in the near future. Analyses of the normal electroencephalograms made with leads on the left occipital area and on the ear reveal that energy is scattered over all frequencies from below 1 to approximately 60 cycles per sec., a range in which we are particularly interested. But more energy is found at cer-

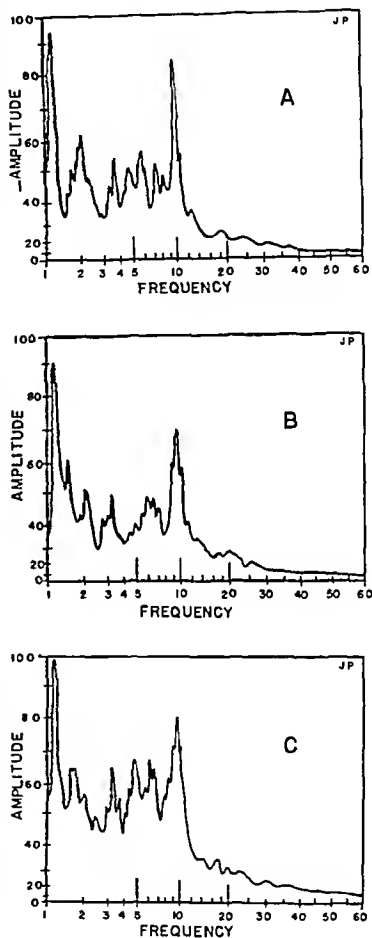


FIG. 5

ANALYSES OF A NORMAL'S RECORDS AT  
TWO DAY INTERVALS

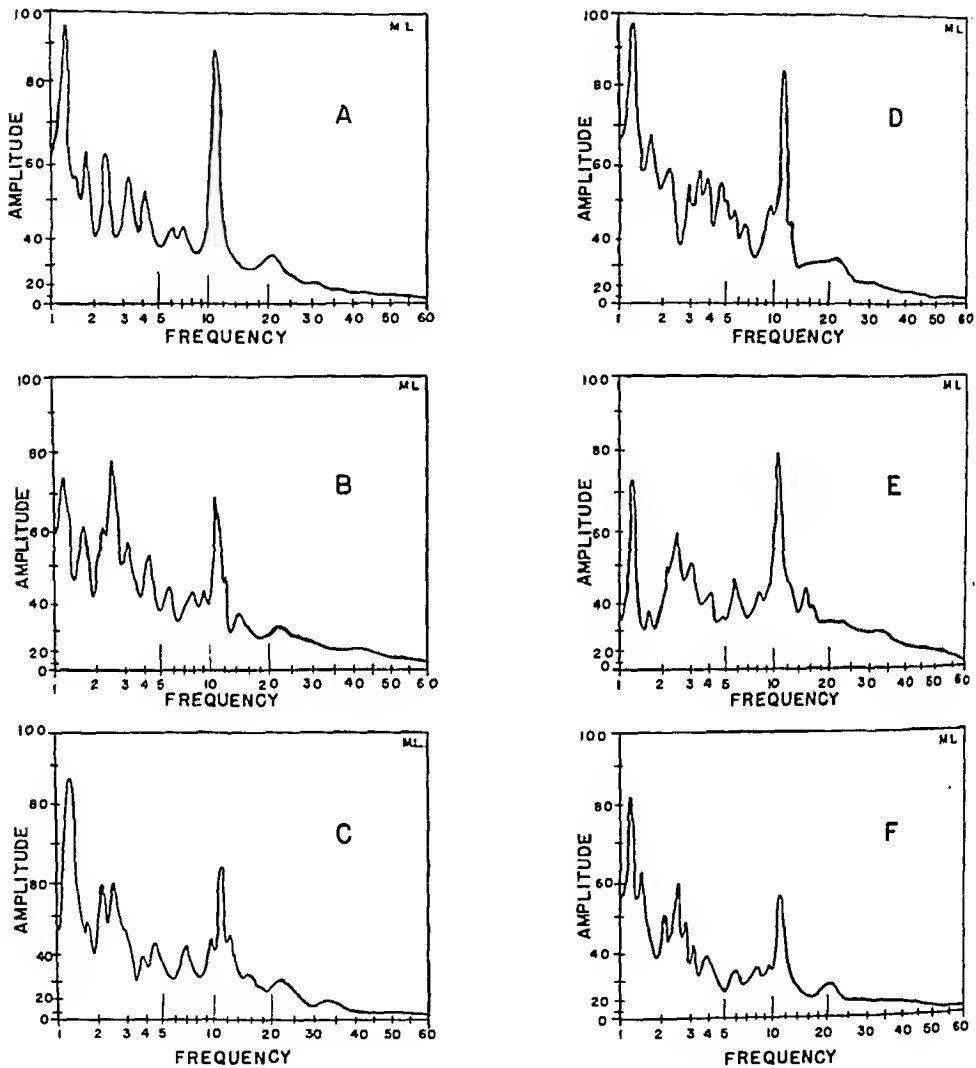


FIG. 4

ANALYSES OF RECORDS OF A NORMAL TAKEN AT 10 MINUTE INTERVALS

# THE INFLUENCE OF CYANIDE ON BRAIN POTENTIALS IN MAN

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PORTER, Blair and Bohmfalk (1938) report that NaCN has a facilitating effect on motoneurons in the spinal cord of the cat. It occurred to us that cyanide might be useful for studying the behavior of cells in the cerebral cortex of man. NaCN is a strong respiratory stimulant in sub-convulsive doses (Loevenhart, *et al*, 1918), the carotid sinus being its site of primary action (Heymans, Bouckaert and Doutrebande, 1931). Thus cyanide may be used safely in man, with the special advantage that one can readily ascertain when it reaches the carotid sinus, and, consequently, when it can be expected to reach the brain.

## METHODS

to-  
an-  
patients A group of 19 patients were given intravenous injections of 0.7 cc. of 2 per cent solution of NaCN (equivalent to 14 milligrams) via the antecubital vein near the elbow. In addition, the effect of cyanide on the electroencephalograms of a narcoleptic and a stuporous catatonic were observed.

Brain potentials were recorded on paper tape from electrodes placed on the scalp over various cortical regions, suitable amplifiers being used. A more detailed description of the recording technique may be found elsewhere (Rubin, 1938).

## RESULTS

NaCN in the doses used here produced a series of deep gasps which occurred from 15 to 20 secs. after the injection and lasted for 10 to 20 secs. The following brain potential responses most frequently took place immediately after the respiratory response ceased or, in some cases, not until as much as 30 secs. later. The time for full return to the pre-NaCN level of cortical activity was usually about 2 mins. There seemed to be no relation between the severity or duration of the respiratory response induced by cyanide and the resulting brain potential changes.

In 12 patients out of 19 an increase in amplitude, regularity and amount of alpha (10/sec.) activity was observed, followed in a few instances by a decrease. In addition, higher frequencies became more predominant and slow irregular rhythms tended to disappear. Frequency remained unaltered. An initial, slight depression of alpha activity was observed in three subjects, followed in one case by an increase above the pre-NaCN level. The other four patients showed no change in their electroencephalograms.

It is well known that the first effect of cyanide is an excitatory one, if the concentration is not too great; in still higher concentrations it is a depressant

agent. It is reasonable to suppose that in the three subjects who showed a depression of cortical activity, the concentration of cyanide was considerably greater than that which would have resulted in excitation for those individuals. Unfortunately, we did not try different dosages of NaCN, but used the same amount for all subjects. It is possible that the cyanide dosage was below threshold for the four individuals whose brain potentials remained unaltered.

The general response to NaCN seems to be an increase of activity in cortical cells which are capable of producing the alpha rhythm, and greater regularity of the rhythm. The most marked effects were obtained from the motor region, although the frontal lobes tended to be equally affected. The parietal

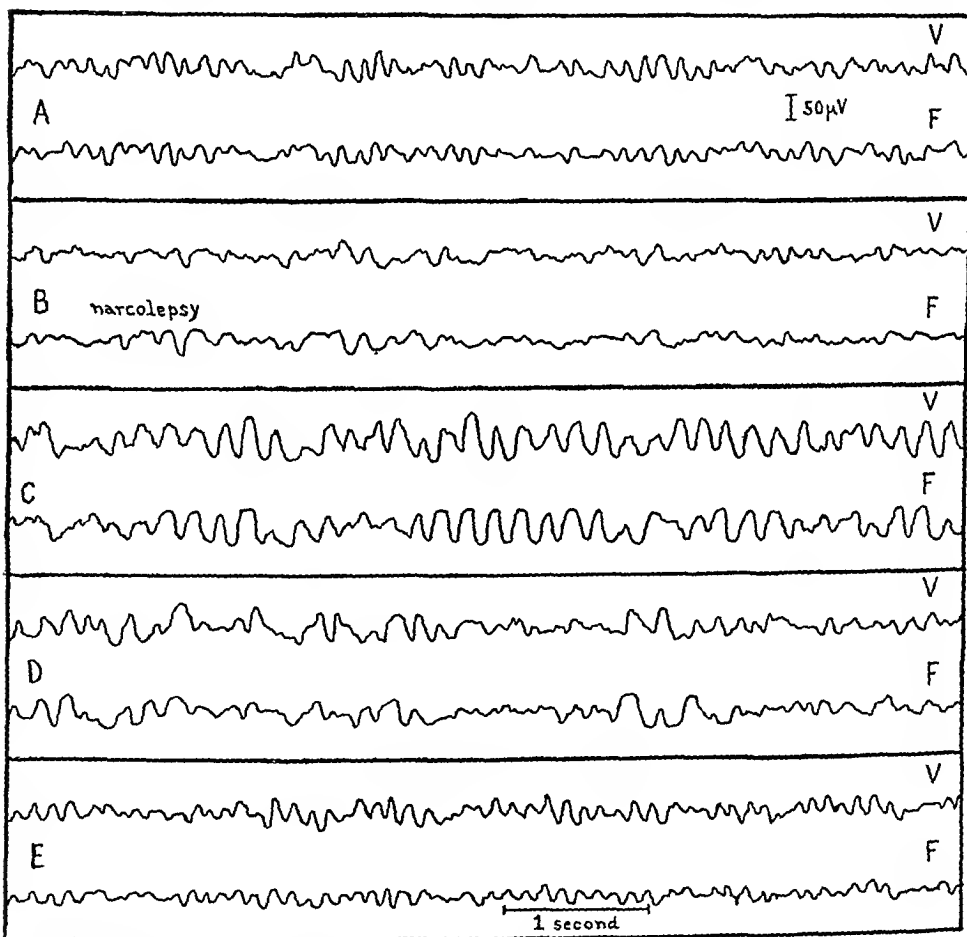


FIG. 1. Simultaneous records from midline electrodes on the vertex (V) and over the mid-frontal (F) region of a narcoleptic. A was taken when the subject first reclined on the bed; B is typical of the narcoleptic state which occurs within a minute or so after the individual lies down; C shows regular 5-6 per sec. waves appearing 20 secs. after stimulation of the carotid sinus by NaCN; D, one-half minute later; E, one minute after D. Amplification constant throughout.

region was least responsive to NaCN, and the occipital alpha rhythm was the most variable, showing no change, an increase or a decrease

The effect of NaCN on the brain potentials of a narcoleptic individual proved of considerable interest (Fig 1) In the waking state his alpha rhythm had a frequency of 8 to 9 per sec, during the narcoleptic state the alpha rhythm was markedly decreased in voltage, only slower frequencies remaining unaltered After intravenous NaCN, regular 5 to 6 per sec waves of higher voltage appeared, to be followed later by an irregular potential pattern Finally, in 2 minutes, the initial pattern was reestablished

A more dramatic illustration of the increased tendency towards slower rhythms was observed in a catatonic individual who occasionally went into a stuporous state characterized by failure to perform any voluntary movement He was fully conscious at all times and had perfect recollection of events which took place during his stuporous periods In this case stupor was accompanied by a diminution of amplitude of the alpha rhythm and the amount of time it was present (Fig 2, A and B) One-half a minute after the respiratory response induced by NaCN was over, a rather regular 4 per sec rhythm suddenly appeared under both the occipital and vertex electrodes This was followed by irregular bursts of activity with occasional regular periods of slow activity for the next 4 mins Although the slow rhythm was similar to that described for some epileptics by Gibbs, Gibbs and Lennox (1937), we observed no clinical signs of a seizure associated with it

Control experiments in which this stuporous individual was given 0.7 cc of distilled water, instead of NaCN, and also painful stimuli, failed to produce any cortical response Several days later when he came out of stupor spontaneously cyanide induced changes in his electroencephalogram similar to those described previously for the group of 19 subjects

## DISCUSSION

Several possible explanations of the cortical effect of NaCN are worth considering

1 *Cardiovascular changes*—The increases in blood pressure and pulse rate following cyanide injection are rather small and could hardly be expected to influence cortical activity In addition, it is difficult to reconcile a unidirectional cardiovascular change with both slow and fast cortical potentials

2 *pH changes*—Gesell, *et al* (1930) reported a decrease in blood pH on injection of NaCN into animals If this caused a decrease in pH of the cerebral cortex we should expect to find a decrease in frequency and amplitude of cortical potentials (Dusser de Barenne, McCulloch and Nims, 1937) This would not account for the observed increase in amplitude of the alpha waves and the absence of alteration of their frequency. It would account for the slow rhythms found in our narcoleptic and stuporous catatonic subjects but not for the increased amplitude of these slow waves

3 *Hyperventilation*—It is questionable whether sufficient hyperventilation occurred as a result of the respiratory stimulation by the NaCN Hyperventi-

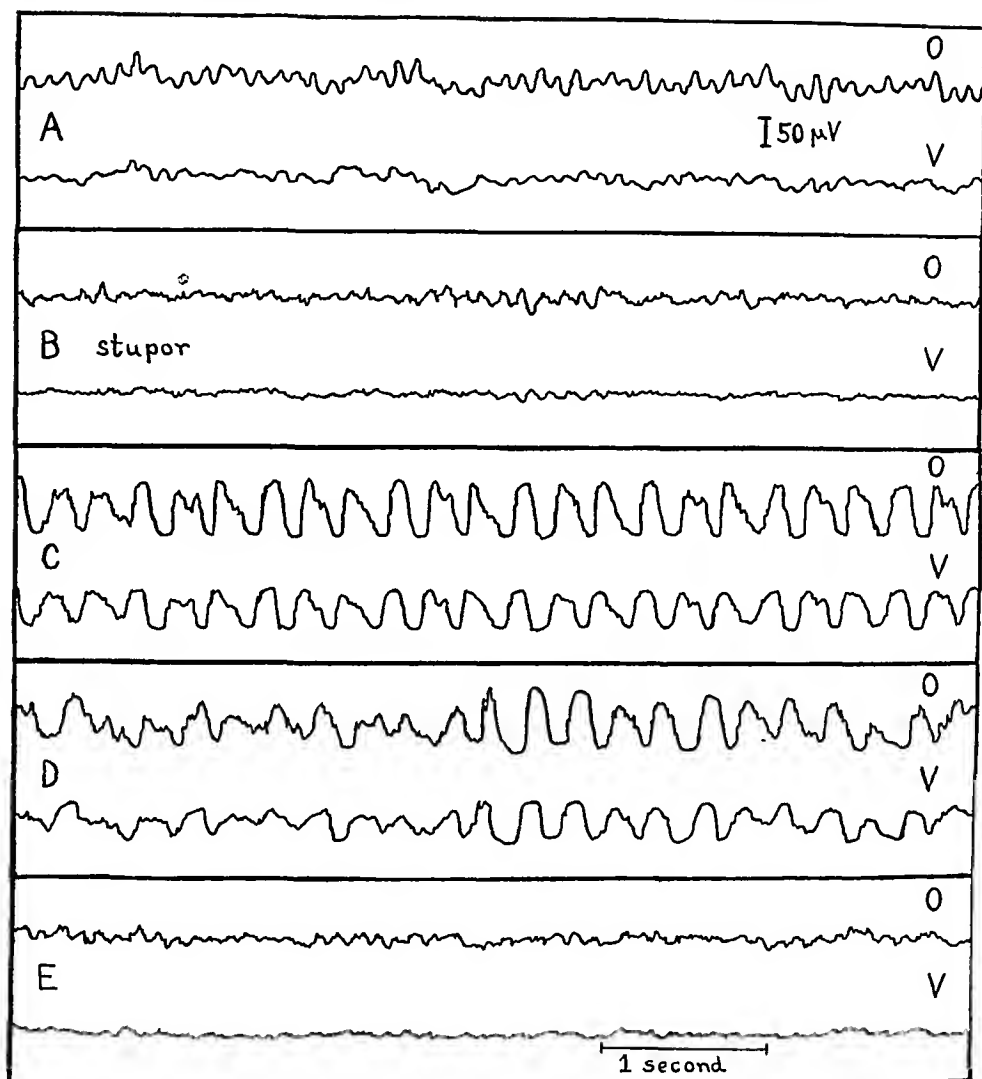


FIG. 2. Simultaneous records from the occiput (O) and the vertex (V), along the mid-line, from a patient in a catatonic stupor. A, a typical record from this patient when he was not stuporous; B, during stupor and before NaCN was given; C, 30 secs. after the gasping due to intravenous NaCN was over; D, 30 secs. later, illustrating the irregular pattern and an occasional period of regularity; E, at the end of 5 mins. The amplification is the same throughout.

lation, if it were marked enough, would cause an increase in pH of the cortex (Dusser de Barenne, McCulloch and Nims, 1937). However, it is not likely that the pH of the cortex would be increased in the face of a decrease in blood pH. According to Gibbs, Davis and Lennox (1935), the only change in cortical potentials from over-ventilation is the appearance of large 2 to 5 per sec. waves especially when unconsciousness sets in. Our two patients who showed slow

rhythms were not unconscious at any time, and records from the other 19 subjects usually showed less slow activity after NaCN.

It is apparent that the explanation does not lie in the three possibilities just discussed. It is more reasonable to infer that NaCN acts directly on the cortex. As we see it, 15 or 20 secs. after injection of cyanide the carotid sinus is stimulated, setting up afferent impulses to the medulla with subsequent respiratory stimulation. After a lag of another 20 or 30 secs. the cortical response is obtained. The interval between the carotid sinus and the cortical responses must represent the "latent period" of the cortex for the response to cyanide, since the circulation time from carotid sinus to cortex cannot possibly be that long. Porter, Blair and Bohmfalk (1938) give a "latent period" for facilitation in the cat's spinal cord by NaCN of the same order of magnitude, —12 secs., on the average. They concluded that slight asphyxia, due to the NaCN, causes facilitation at the synapses. This would account for the increase in amount and regularity of the cortical alpha rhythm. It might also explain the facilitation of slow rhythms if we assume that cyanide produces synaptic block, rather than facilitation, in a functionally "depressed" cortex. Synaptic block, produced by nicotine, does retard cortical potentials and makes them more regular (Libet and Gerard, 1938). However, the further assumption must be made that "depressed" cortical neurons have a lower threshold to NaCN than normally active neurons, so that concentrations of cyanide which are ordinarily excitatory now become markedly depressant. Such a mechanism would mean that both excitatory and depressant concentrations of cyanide can increase the electrical activity of the cortex and make it more regular.

The importance of the thesis that the pre-existing state of the cortical neurons determines their response at any given time (Blake and Gerard, 1937) is emphasized by our experiments. If the tendency is toward fast activity (i.e., the alpha rhythm) NaCN will enhance it; on the other hand, when the cortex is functionally "depressed" (as in narcolepsy and in catatonic stupor) slow activity, characteristic of subnormal cortical activity, is increased by cyanide.

#### SUMMARY

Sodium cyanide was injected intravenously into 19 adult male subjects and the resulting changes in potentials from the cerebral cortex were recorded. In general, the alpha rhythm was enhanced, showing an increase in amount of activity, amplitude and regularity. In one narcoleptic and one stuporous catatonic patient, NaCN injection resulted in the appearance of regular, large slow waves. Both effects are interpreted as due to the direct action of NaCN on cortical neurons. The type of response (whether facilitation of fast or of slow rhythms) depends on the pre-existing state of the cortical elements.

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# CERTAIN EFFECTS OF PROLONGED STIMULATION OF AFFERENT NERVES ON THE REFLEXES EVOKED

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It is a common observation that the strength of the reflex contraction of a striated muscle changes during prolonged stimulation of the afferent nerve, and that if the frequency of stimulation is not too low, the response tends to subside even during stimulation of maximal intensity. A number of workers have investigated the effect of continued stimulation of one afferent nerve on the response of the affected muscles to stimulation of a second afferent. Reflex movements of the hind legs evoked from different skin areas in the strychninized spinal frog were studied by Verworn (1901), and the elicitation of the scratch reflex in the spinal cat and dog by Sherrington (1906). The flexor reflex has been investigated by Lee and Everingham (1909), Forbes (1912), Upland and Michelson (1933), and others; and inhibition of the contralateral extensor by Forbes (1912). The general conclusions of these authors were that subsidence of the response was due to central "fatigue" or "pseudofatigue," and that such "fatigue" of one afferent system did not necessarily affect another afferent system.

If this "fatigue" were of the nature of "exhaustion" at the synapse and if it occurred generally, it would offer a further means for analysis of the spinal and medullary reflex mechanisms. It therefore seemed desirable to extend the observations to other reflexes.

## METHODS

Cats were used throughout and were prepared by transection of the spinal cord at T6 or T12, one to eighteen hours before the experiment, or by anaemic or trephine decerebration. In a few cases one of the barbiturate anaesthetics or urethane was given in addition. For observations on the responses from stimulation of the motor cortex the animals were anaesthetized with Dial Ciba, 0.7 cc per kg. Reflexes of the hind legs only were studied and particular attention was paid to the ipsilateral flexor (tibialis anticus and gracilis) and the inhibition of the knee jerk. Observations were also made on the ipsi- and contralateral extensors (quadriceps and gastrocnemius soleus) and the contralateral flexors. Immobilization and fixation were by nerve and tendon section and drills in the bones. Muscular contraction was recorded on a smoked drum by means of levers with heavy rubber bands, or optically by a Sherrington torsion wire myograph. For afferent stimulation electrodes were applied to appropriate peripheral nerves (hamstrings, peroneal, popliteal, femoral), to posterior roots (6th, 7th and 8th lumbar), or to the motor cortex. Several different types of electrodes were tried. The most consistent results were obtained with silver-silver chloride electrodes applied directly to the nerve or through a Ringer's solution-agar bridge. The stimulating current consisted of 60 cycle a.c. through a step-down transformer and potentiometer and of short, diphasic shocks from a photo electric cell stimulator with a frequency range of 1 to 360 per sec.

Stimulation was always of such strength as to elicit maximal responses. To test the adequacy of the stimulus several devices were used, including increase in the strength of

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the stimulating current, moving the electrodes proximally along the nerve or testing with a second pair of more proximal electrodes. Improvement in the response indicated inadequate stimulus. To control for changes occurring in the muscle the motor nerve was maximally stimulated before and after observations on the reflexes.

The procedure in general was as follows. The muscle was prepared for recording, and stimulating electrodes were applied to two afferent nerves. One afferent was stimulated with a tetanizing current at frequencies of 30 to 360 per sec. continuously for periods of 2 to over 20 min. in different observations. (This will be designated as the *prolonged stimulus* hereafter.) The other afferent was stimulated either by single shocks or by short tetani, 3 to 5 secs., in such a manner and at such intervals as to evoke a constant response. (This will be designated as the *test stimulus* or *test reflex* hereafter). The course of the reflex elicited by the prolonged stimulus and the effect of the prolonged stimulus on the test reflex were noted.

## RESULTS

Consistent and reproducible results were obtained over periods of 4 to 5 hours in the spinal preparations. With decerebrate preparations, however, it was often only possible to make 2 or 3 observations, following which the pulse became rapid and feeble, respiration gasping and all reflex activity depressed. This was particularly marked in cases which showed considerable generalized activity during stimulation. In cats under "dial" with intact central nervous system, the response to the initial stimulus was stronger than that to succeeding stimuli unless a period of more than 30 minutes' rest intervened, after which another large response was obtained.

In general two types of behavior of the reflexes resulted from prolonged stimulation: (i) rapid subsidence of the prolonged reflex, with little or no change in the test reflex; (ii) continued reflex activity of both inhibitory and excitatory nature throughout the period of adequate stimulation of the afferent nerve, with modification of the test reflex during and following this period. The former was exemplified best by the flexor reflex, the latter by inhibition of the knee jerk.

*Flexor reflex.* The results on the flexor reflex coincided with those interpreted as central "fatigue" by previous workers and need not be described in detail. At frequencies of stimulation above 60 per sec. the reflex contraction subsided in 30 secs. to 3 mins. in spinal and decerebrate preparations without anaesthesia, and in 3 to 20 secs. in preparations under dial. Facilitation of the test reflex could be demonstrated for a longer period, usually 1 to 2 mins. After facilitation had also subsided, the test reflex was evoked, in the majority of instances, as in the preliminary control period, and cessation of the prolonged stimulation had no further effect. In a few experiments the test reflex was diminished following the prolonged stimulation. That a considerable proportion of the motor neurons involved in the reflexes were stimulated by both afferents was demonstrated by the phenomenon of occlusion, and in several cases by the fact that each afferent evoked a reflex response which was 60 to 80 per cent of the contraction resulting from stimulation of the whole motor nerve at the same frequency.

This type of independence of the reflex arcs was readily demonstrated for the flexor reflex when either peripheral nerves or posterior roots were used as afferents. The contralateral flexor and the ipsilateral extensor also behaved in

the same way. On rare occasions a similar phenomenon was observed when the test response was elicited by stimulation of the motor cortex, and also rarely in the experiments on other reflexes. In the great majority of the latter experiments, however, quite variable results were obtained, which may be illustrated by the following examples of inhibition of the knee jerk.

*Inhibition of the knee jerk.* In several experiments on inhibition of the knee jerk the initial response was of the type illustrated in Fig. 1, but in no case was this result obtained after a preparation had been subjected to 2 or 3 periods of stimulation. The characteristic features were as follows. At the beginning of prolonged stimulation the knee jerk was inhibited and the muscle contracted in a more or less smooth tetanus, an ipsilateral extensor reflex. After a few seconds the knee jerk reappeared and was not inhibited again by increasing the intensity of stimulation (at the arrow in Fig. 1). That is, the knee jerk reappeared in the presence of apparent maximal stimulation

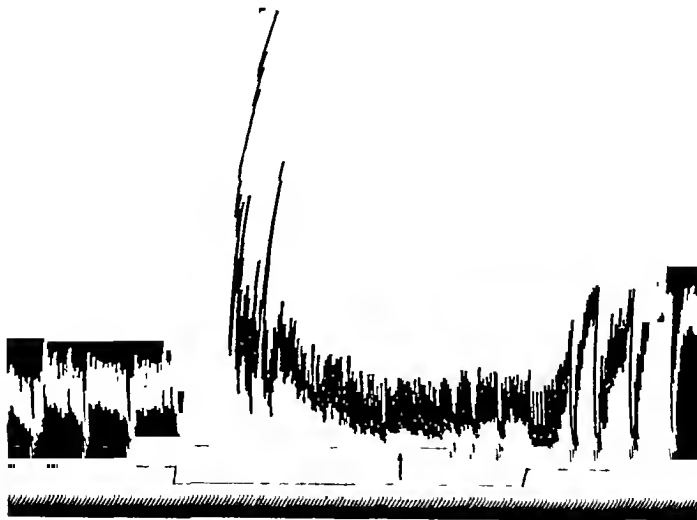


FIG. 1. 3/4/38. Cat, male, 12 hours after transection of the spinal cord at T6. Left quadriceps recording. Knee jerks elicited by electrical hammer twice per second. Upper signal. Single shocks to left peroneal 66 $\sigma$  before next succeeding knee jerk. Photo-clectric cell stimulator, 30 volts. Middle signal. Prolonged stimulation of left popliteal, 60 cycle a.c., 5 volts, increased to 10 volts at arrow,  $\uparrow$ . Lower signal. Time in seconds. The flattening of the record at the top of the ipsilateral extensor reflex was due to mechanical interference.

of the afferent nerve. The reappearance of the knee jerk usually occurred when the ipsilateral extensor contraction was at its maximum or had begun to subside. Throughout the period of stimulation there was evidence of continued inhibitory activity (depression of the level of clonus and a short inhibitory after-discharge in the case illustrated). Following a latent period of variable duration on cessation of stimulation a strong rebound contraction occurred which demonstrated the presence of excitatory as well as inhibitory activity during stimulation.

In the example given the test stimuli (single shocks to the peroneal) were equally effective before the prolonged stimulus, after the reappearance of the knee jerk, and during the post-stimulatory rebound contraction, indicating an independence of afferent systems.

In other experiments in which the strength of the ipsilateral extensor contraction was less than that of the knee jerk, it was clear that the latter was inhibited and not occluded during the early phase of the former. Also the effect of the second afferent was to facilitate and not to inhibit the ipsilateral extensor. In both of these respects the ipsilateral extensor and the post-stimulatory rebound contraction appeared to be different phenomena, probably with separate central neural mechanisms.

The common type of response during prolonged inhibition of the knee jerk is illustrated in Fig. 2. This record was selected because it shows the essential features in short compass. Similar results, excepting the two sudden strong contractions during the terminal period of stimulation, were obtained in experiments in which the strength of the stimulating current was gradually increased from 2 to 50 volts over a period of 15 to 20 mins. The presence or absence of clonus or of irregularity of the knee jerk, as in Fig. 2, during the preliminary period did not affect the course of the reaction. At the beginning of prolonged stimulation there was complete inhibition of the knee jerk lasting from 4 or 5 to 50 or 60 secs., and usually a small ipsilateral extensor response. The knee jerk then reappeared, sometimes weak and irregular, sometimes rapidly becoming strong. Increasing the strength of the stimulating current (at the arrow in Fig. 2), or moving the electrodes proximally on the nerve, abolished the knee jerk again for a further period. This could be repeated to the limit of the strengths of current used (50 volts) or to the limit of the length of nerve available. Similar results were obtained with frequencies from 60 to 240 per sec., the duration of the periods of effective inhibition decreasing with increase in frequency. Increasing the intensity of stimulation by large increments did not proportionately prolong the periods of inhibition. The quantitative relationships of these factors were not investigated due to the fact that with repeated stimulation other changes occurred in the preparation as described below. The duration of the excitatory after-discharge varied in different preparations from 1 or 2 to over 40 mins. In general the decerebrate preparations showed greater excitatory after-discharge than the spinal, but the two groups overlapped in this regard and the general condition of the animal appeared to be as important a factor as the level of transection. In



FIG. 2. 2/28/38. Cat, male, 18 hours after transection of spinal cord at T6.

Record and signals as in Fig. 1, except stimulus to popliteal nerve 12 volts, increased to 20 volts at arrow, ↑.

some cases the after-discharge did not appear unless the prolonged stimulation was of at least 2 minutes' duration, but in the majority of instances it appeared after a succession of short (10 to 15 secs.) tetani.

The response of the test reflex in the group of experiments under consideration varied greatly from preparation to preparation. In some there was little change of either the excitatory (ipsilateral extensor) or inhibitory action. In this respect the results indicated a certain independence of the reflex arcs, as was found for the flexor reflex. In other preparations, however, considerable changes of long duration occurred, an example of which is illustrated in Fig. 3. Early in this experiment, Fig. 3A, the ipsilateral extensor response, evoked by a single shock to the peroneal nerve, was small and the after-discharge of inhibition of the knee jerk was profound and long. Figure 3B is a portion of the record during prolonged stimulation of the popliteal nerve, the voltage having been gradually increased whenever the knee jerk reappeared (e.g., from 25 to 27 volts at the arrow). A single shock to the peroneal after 3 minutes' stimulation of the popliteal showed a stronger ipsilateral

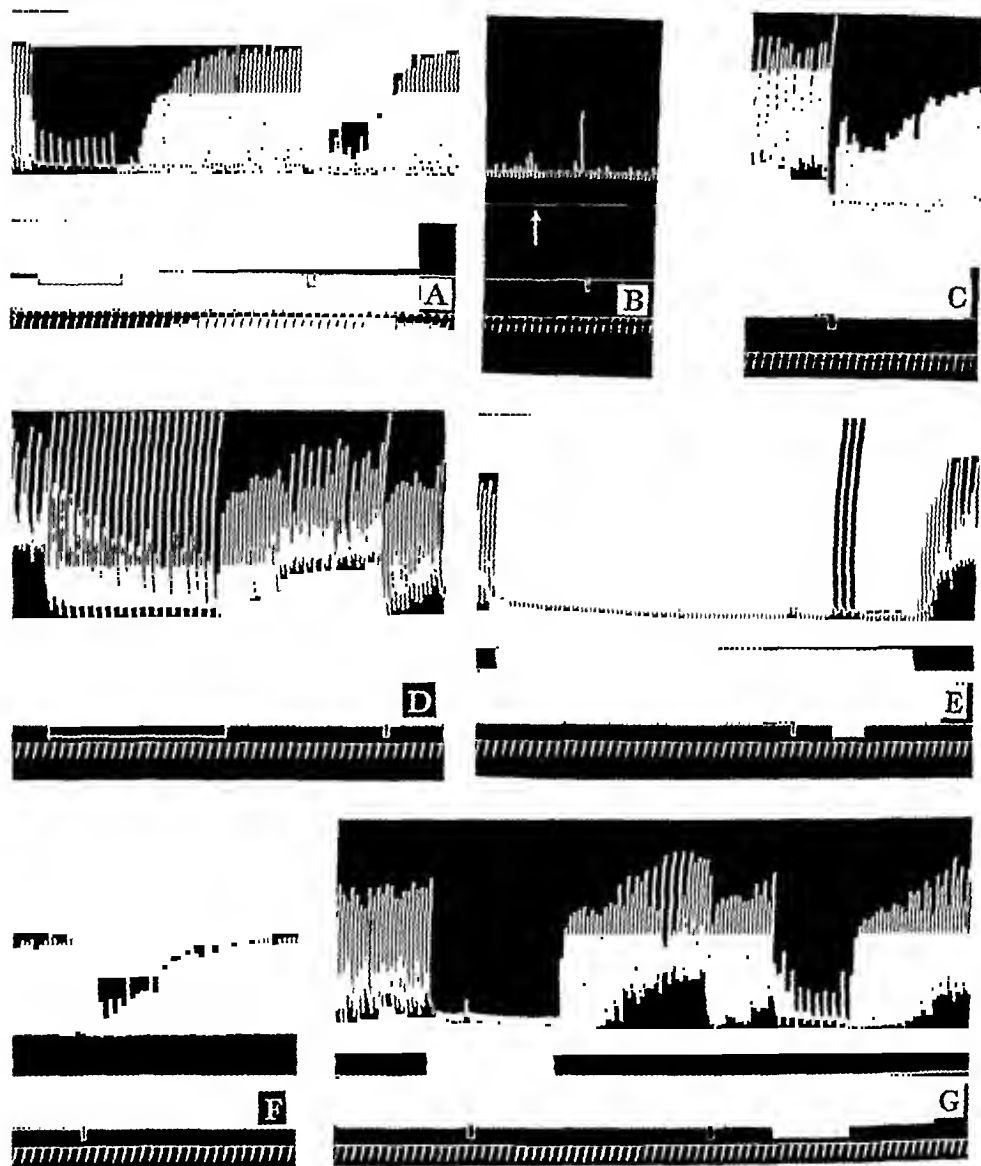


FIG. 3. 2/24/38. Cat, male, 18 hours after transection of spinal cord at T6.

Record as in Fig. 1. Upper signal. Prolonged stimulation of left popliteal, 60 cycle a.c. Voltage increased from 25 to 27 volts at arrow,  $\uparrow$ , in B. 30 volts in E and G. Middle signal. A single shock or a series of shocks at 1 per sec., 66 $\sigma$  before the next succeeding knee jerk to the left peroneal. Photo-electric cell stimulator, 40 volts. Lower signal. Time in seconds. For further description see text.

extensor contraction. C, D and E were recorded  $6\frac{1}{2}$  mins. later, during which time two periods of stimulation of 1 min. each intervened. The ipsilateral reponse was much stronger, the inhibition weaker and its after-discharge shorter, particularly during the clonus in D. Thirty-eight minutes without stimulation elapsed between E and F. After this rest period the responses (Fig. 3, F and G) more closely resembled those at the beginning of the experiment (A and B), but the development of clonus and the curtailment of inhibitory after-discharge to a single shock during clonus in G indicated that the activity built up before the rest period had not yet subsided. This illustration was an extreme case, but similar changes of smaller magnitude were common.

A third type of behavior of reflex responses during and following prolonged stimulation was seen less frequently. It usually appeared in preparations in which the general reactivity was low, during the late stages of a long experiment, and in preparations which received barbiturate anaesthetics. In this type of response the ipsilateral extensor contraction was usually absent or, at best, very weak. During stimulation at frequencies of 60 and 120 at voltages of 15 to 30 for as long as 22 mins. there was no reappearance of the knee jerk and at the termination of stimulation there was little or no rebound contraction. The test reflex was essentially unaffected by the prolonged stimulation.

*Contralateral extensor and other reflexes.* In animals decerebrated by the trephine or anemic methods stimulation of the contralateral nerves evoked a number of reflexes. Extensor contraction was the usual response, but, particularly with the second method of preparation, flexor contraction and inhibition of the extensors with or without rebound contraction were not infrequent. The results of these experiments, as well as of the experiments on inhibition of the contralateral extensor and on facilitation of the contralateral motor cortex by an ipsilateral nerve, may be summarized as follows.

The contralateral flexor reflex behaved in a manner similar to that of the ipsilateral flexor described above. Reflex inhibition of the contralateral extensor showed little tendency to subside during stimulation, but it was not followed by so prolonged a rebound contraction as was reflex inhibition of the knee jerk. Rapid subsidence of the other reflexes during continuous tetanization was rare. In the majority of instances they only partially subsided as long as the afferent nerve was adequately stimulated (frequencies of 30 to 360 were used), and modification of the test reflex continued for periods up to 4 or 5 mins. after the prolonged stimulation was terminated. Changes of long duration, 30 to 40 mins., such as that illustrated in Fig. 3, were not encountered. The modification of the test reflex was always most marked and sometimes only present in its after-discharge.

An example of the responses of the quadriceps to stimulation of contralateral nerves is shown in Fig. 4. The test reflex, A, showed inhibition during stimulation of the contralateral femoral and rebound contraction with relatively long after-discharge. The beginning of prolonged stimulation of the



contralateral sciatic is shown in B with the resulting contraction of the quadriceps. This was not completely inhibited during the test stimulus, but was enhanced by the rebound. Stimulation of the sciatic was continued for 15 mins. between B and C. The prolonged reflex had only partially subsided and there was facilitation of the rebound contraction of the test reflex, though the inhibitory component during stimulation was as complete as in A. Eleven secs. after cessation of sciatic stimulation the inhibitory component of the test reflex appeared unchanged, but the rebound contraction was markedly reduced. In 4 mins. the test reflex recovered.

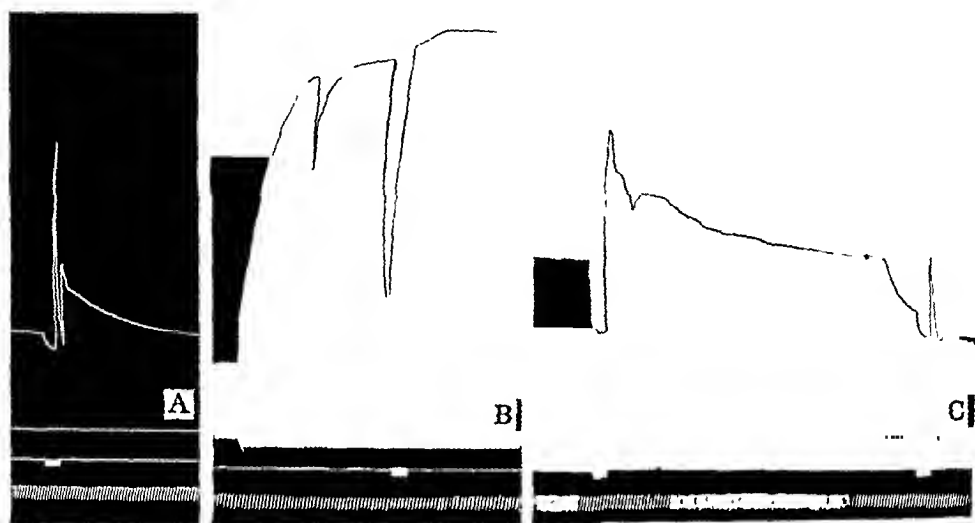


FIG. 4. 9/14/37. Cat, male, anemic decerebration.

Left quadriceps recording. Upper signal. Prolonged stimulation of right femoral. Diphasic shocks, 1 $\sigma$  duration, from the photo-electric cell stimulator through a 1:1 transformer, 45 volts, 60 per sec. Middle signal. Stimulation of right sciatic for 5 second intervals. 60 cycle a.c., 3 volts. Lower signal. Time in seconds. For further description see text.

## DISCUSSION

As stated in the introduction, the phenomenon of subsidence of a reflex during continued stimulation has been generally interpreted as being due to a central "fatigue." This sounds plausible, but gives no clue to the nature of the mechanism involved. In a number of experiments (*cf.* those of Upland and Michelson, and also those described on page 536, Fig. 2 above) the subsidence was apparently due to inadequate stimulation, following the change of threshold of the afferent nerve during activity. In other cases, *e.g.*, in the experiment illustrated in Fig. 1, the phenomenon appeared to be due to reflex activity of opposite sign, possibly evoked by different fibers in the mixed afferent nerve. Another example of this is the short maintenance of the flexor reflex under barbiturate anaesthesia, the inhibitory mechanisms being relatively more effective with drugs of this group (Bremer and Moldaver,

1933). It is indeed probable that both of these factors, namely, cessation of activity in the afferent system peripherally, and reflex activity of opposite sign centrally, play a rôle in most if not in all cases of so-called central "fatigue."

In the experiments reported here subsidence of central inhibitory activity only appeared in the presence of a strong excitatory component from the stimulation of the mixed afferent nerve, and "fatigue" or "exhaustion" or reflex inhibition did not occur. This apparent non-fatigability of inhibitory processes does not constitute a qualitative difference between them and the excitatory processes. If it did, one would have to assume that no internuncial neurons were present in the organization involved in reflex inhibition, which is highly unlikely. Further, the experiments on inhibition of the knee jerk (p. 535) showed that the excitatory activity elicited by the prolonged stimulation was as resistant to "fatigue" as was the inhibitory. The observations on the contralateral extensor and other reflexes (p. 539) may be similarly interpreted. The presence of profound inhibition and the absence of excitation in preparations in poor condition or under barbiturate anaesthesia (p. 539) constitute negative evidence with regard to the problem at hand, but suggest differences in metabolic and other chemical properties of the neurons or synapses involved. It may therefore only be stated that in certain reflex systems the central activity, whether inhibitory, excitatory or both, does not subside or "fatigue" as long as the afferent fibers are adequately stimulated for durations of 15 to 20 mins. and at frequencies up to 360 per sec.

The specificity and independence of the afferent paths of the reflex arcs demonstrated by the present experiments may be accounted for by assuming specific and independent internuncial neurons. Moreover, the fact that certain collaterals of the dorsal root fibers end on the anterior horn cells suggests that the synapses are themselves independent units.

No generalization can be made at present about the nature of the reflexes which show rapid subsidence as contrasted with those which do not, or about the properties of the neurons involved in their organization. It is not a function of the dominance of the reflex as measured by its capacity to preempt the final common path, nor a function of the number of synapses in the reflex arc (*cf.* the flexor reflex, which subsides rapidly, and the contralateral extensor, which is well maintained). Certain teleological explanations may be given, but definite data are lacking. In the present series of experiments the reflexes which subsided rapidly were the ipsi- and contralateral flexor and the ipsilateral extensor; those which were well maintained included the contralateral extensor, inhibition of the knee jerk, rebound contraction of the quadriceps following inhibition of the knee jerk, and, in cats under dial, facilitation of the contralateral motor cortex by an ipsilateral nerve.

In conclusion it may be pointed out that, although there appears to be considerable variability in the responses of spinal and decerebrate preparations to stimulation of peripheral afferent nerves, in a long series of experiments these different responses may be grouped into rather specific types.

Among the numerous factors which combine to determine the type of response evoked, the duration and intensity of previous stimulation, hence the technique of preparation, must be considered. The more standardized the technique becomes the more consistent will be the responses evoked, and also, frequently, the more dogmatic the conclusions drawn.

### SUMMARY

Certain reflexes of the hind legs of spinal and decerebrate cats, and occasionally of cats under barbiturate anaesthesia, were studied myographically. One afferent nerve was maximally stimulated at frequencies of 30 to 360 per sec. for periods of 1 to over 20 mins. Another afferent was stimulated intermittently in such a manner as to evoke a standard response.

The ipsi- and contralateral flexor and the ipsilateral extensor reflexes subsided completely during the prolonged stimulation. In many cases the standard response was unchanged by the prolonged stimulation, in other cases it was slightly reduced. These results demonstrate a certain degree of independence of the afferent paths of the reflex arcs.

Other reflexes, including the contralateral extensor, inhibition of the knee jerk, rebound contraction of the quadriceps following inhibition of the knee jerk, and facilitation of the response from the contralateral motor cortex by an ipsilateral nerve, showed the same type of behavior on rare occasions. Commonly, however, the reflex did not completely subside as long as the afferent nerve was adequately stimulated. The standard response from the second afferent in these cases showed great variation, remaining unchanged in some but usually being either facilitated or inhibited both during the prolonged stimulation and for periods of 2 or 3 to over 40 mins. afterwards.

It is pointed out that in many cases subsidence of a reflex response is due wholly or in part to inadequate stimulation of the peripheral afferent nerve, or to central reflex activity of opposite sign, and that in certain central nervous system mechanisms reflex activity, both excitatory and inhibitory, continues as long as the afferent nerve is adequately stimulated.

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# SEPARATION IN THE BRAIN STEM OF THE MECHANISMS OF HEAT LOSS FROM THOSE OF HEAT PRODUCTION\*

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## INTRODUCTION

THE MAINTENANCE of a constant body temperature in animals having the power of heat regulation is due to the delicate balancing of activity of two quite distinct physiological mechanisms. One, commonly spoken of as the mechanism of "heat loss" (or "heat dissipation"), prevents undue rise of body temperature by facilitating the dissipation of heat, and possibly also, by reducing metabolic heat. The other mechanism, commonly spoken of as that of "heat production," prevents undue fall of body temperature by increasing the heat produced, as well as by restricting the dissipation of bodily heat. It has often been assumed that the various peripheral structures concerned in each reaction are controlled by the same central mechanism. The alternative possibility of each being to a degree independently regulated by discrete central mechanisms was implicit in Meyers' original hypothesis concerning heat regulation; to quote Hasama:<sup>1</sup> "the thermo-regulatory adjustment of warm blooded animals is affected through a sympathetic thermogenic 'warm center' as well as through a parasympathetic thermolytic 'cold center'." With regard to the central representation of these mechanisms Hasama states, "whether the two are morphologically separable or not we do not know, but they are apparently distinct and discrete functionally, inasmuch as they control each other antagonistically, and thus balance each other."

During the past several years evidence has accumulated which indicates a certain central structural and functional independence of these two mechanisms. I have described various procedures whereby in acute, as well as in chronic, cats and dogs, the mechanisms regulating heat production can be essentially eliminated, leaving certain components of the mechanisms regulating heat loss (panting and vasodilation) still intact.<sup>2 3 4 5 6</sup> The opposite situation, the more or less selective elimination of the mechanisms regulating heat loss with a sparing of the mechanisms regulating heat production, has been described by Bazett, Alpers, and Erb<sup>7</sup> in the cat, Teague and Ranson<sup>8</sup> in the cat, and Ranson, Fisher, and Ingram in the monkey.<sup>9</sup>

\* The acute experiments involving transection at the pontile and thalamic levels were performed in the Laboratory of Physiology, Yale University School of Medicine in 1929-1931. The work based on chronic preparations was carried out in Alabama, and was aided by grants from the Committee on Scientific Research of the American Medical Association and from the Rockefeller Foundation

The present paper extends my earlier findings with additional observations on the efficiency of the mechanisms regulating heat loss in these preparations, and it supplements the preliminary reports of this early work.<sup>2,3,4</sup>

#### PROCEDURES

The various surgical approaches to the brain stem and the method of placing lesions have been described elsewhere.<sup>6</sup> The animals' ability to prevent a fall in body temperature was determined by subjecting them to: (i) ordinary room temperatures, (ii) refrigerated box temperature ranging from 0° to 10°C., and (iii) out-of-door extremes during the winter months. Apart from observing rectal temperature under these conditions, observations were also made relative to the presence or absence of shivering. The methods used to test the preparations' ability to prevent a rise in body temperature were exposing them to: (i) a heat beam from an electric heater, (ii) a heated box with a glass door for observation, and (iii) the extremes of warm weather during the summer months. The presence or absence of sweating and of panting were noted under all conditions. During heating tests in the acute experiments, respiratory rates were recorded on smoked paper by means of pneumograph. At the termination of the chronic experiments, as well as in most of the acute, the block of the brain stem containing the lesion was sectioned serially, usually at 10 $\mu$ , and two alternate series of every 10th section were mounted. One set was stained for fiber tracts by a medullary sheath stain, and the other for cells with cresyl violet.

#### RESULTS

##### *Medial transverse section of brain stem in upper pons*

*Acute experiments.* In an early series of acute and subacute experiments where bilateral medial transverse lesions of various widths were placed in the brain stem at the level of the pons, it was found that the ability to regulate body temperature was not impaired until the lateral portions of the brain stem were infringed upon.<sup>2</sup> When wider lesions were made, the animals' ability to maintain temperature became progressively impaired and finally eliminated; so long as a narrow strip of tissue remained on both sides, or even on one side, panting could still be elicited. Panting, however, often did not appear until the rectal temperature was raised above normal. The following are briefs of representative protocols.

*CAT 107—Operation, Dec. 6, 1929.* Following a transverse section (Fig. 1) which cut the entire left medial segment and the greater part of the right medial segment of the brain stem at the middle level of the pons, this cat maintained a normal body temperature for two hours in an icebox at 8°C.; there was conspicuous shivering. When placed in a heated box at 50°C., it did not begin to pant until the rectal temperature reached 40.4°C., at which time typical panting suddenly began and sweat appeared on the pads. The cat was tested on the 7th day after the brain stem lesion.

*CAT 117—Operation, Jan. 11, 1930.* After a lesion wider than that in Cat 107, but at the same general level (Fig. 1), Cat 117 maintained a normal rectal temperature at room temperature, but it fell from 39°C. to 33.8°C. during a period of 1½ hours in an icebox at 5°C., in spite of the presence of slight shivering. When placed in a heated box at 55°C., it did not pant until the rectal temperature had reached 42.2°C. At this time respiration jumped suddenly from 40 to 150 per min. Two minutes later respiration was 245 per min. The cat was tested on the 3rd day after operation.

*CAT 223—Operation, Jan. 18, 1930.* Following the lesion which transected the brain stem completely, save for a narrow strip on the left side (Fig. 1) Cat 223 was unable to maintain its rectal temperature at room temperature, since, when removed from the incubator and placed in an ordinary laboratory room, the rectal temperature rapidly fell to 32°C. without any evidence of shivering. In the heated box, respiration jumped suddenly from 42 to 240 per min. when the rectal temperature reached 40.4°C. The cat was tested on the 3rd day after operation.

*Chronic experiments.* In conjunction with the foregoing acute experiments several questions immediately arose: Was the selective elimination of the mechanism of heat maintenance temporary or permanent in nature? Was a preparation which maintained the ability to pant also able to prevent a rise in body temperature under ordinary conditions of a raised environmental temperature? Were the fibers essential to the panting mechanism limited solely to the extreme lateral segments of the pons? For the solution of these questions it was necessary to turn to chronic preparations. That the heat maintenance mechanism can be permanently and markedly impaired by extensive medial transverse lesions in the upper pons, without materially effecting the heat loss mechanism, is evident from the following experiment (Dog 315-B). The location and extent of the lesion is indicated in Fig. 1.

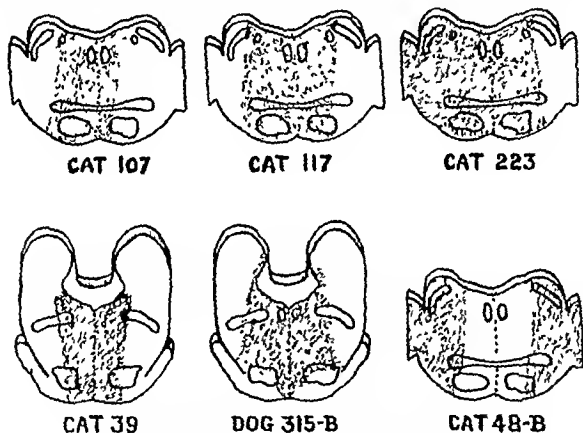


FIG. 1 Drawings showing the location and extent of the lesions in the animals as labeled. For descriptions see text.

*DOG 315-B—Operation, May 15, 1934* By means of a bilateral dorsal exposure of the corpora quadrigemina, a straight, blunt probe was projected downward at the midline through the caudal region of the inferior colliculi and cephalic pons until the bone at the base was reached. The probe was then moved laterally through the tissue of the pons, being withdrawn before the most lateral extent of the brain stem was severed. This procedure was first carried out on the left side and then repeated on the right.

In the chronic state this preparation exhibited an inability to maintain a normal rectal temperature at room temperature, but did keep itself somewhat warmer than the environment. The animal was kept in a room at 20°C. On the 8th day after operation it was

100%) it was

temperature

was never

and 30.5°C

on the 8th, 15th, and 31st days after operation respectively. On the other hand, this dog maintained the ability to pant and to prevent the rectal temperature from rising above a

certain level when subjected to a warm environment. Thus on the 8th day following operation, after being placed in an overheated incubator, vigorous panting began as the rectal temperature reached 40.5°C. The response to the gradual rise of environmental temperature during a warm day is illustrated by its reaction on the 17th day after operation: at 9:00 a.m. the rectal temperature was 38°C., respiration being quiet and regular; at 2:00 p.m. it was 40.2°C.; at 2:40 and at 3:20 the rectal temperature was 39.9°C., typical thermal panting being present periodically. Thus with the onset of panting, a rectal temperature of 40.2°C. was reduced slightly and then maintained, and that without continuous panting. The observations on the 17th day were repeated on several subsequent hot days with the same result. Death occurred the morning of July 2nd (48th day after operation) and a decubitus infection was present. The brain was removed and fixed in formalin. The midbrain-pons block was cut in transverse sections at 20 and every 10th section stained for fiber tracts by the Pal-Weigert method. The lesion had transected the entire brain stem except for the extreme lateral and ventral portions (Fig. 1).

The fact that a lesion must reach well laterally before the mechanisms regulating heat production become impaired was, of course, evident from the acute experiments. This has been verified and emphasized in chronic preparations (cats) having medial transverse lesions at the pontile level. Cat 39 is an example, the location and extent of the lesion being indicated in Fig. 1.

*CAT 39—Operation, Dec., 1931.* The same operative procedure was carried out as in Dog. 315-B. The lesion was at the same cephalic pons level and was of approximately the same width dorsally (the medial half of both brachia conjunctiva being degenerated), but ventrally the lesion was somewhat narrower than that in the dog. The cat survived until June, 1932. This cat maintained a normal rectal temperature immediately following operation and subsequently, even though it was housed in an open cage in a cold (poorly heated) laboratory during the winter months and was out-of-doors during the early spring. Shivering was prominent. Likewise the cat panted typically and sweated profusely when placed in an overheated incubator on the 22nd day after operation. In addition, it prevented a rise in rectal temperature when out-of-doors during the hot days of an Alabama early summer.

The descending fibers governing heat loss are not confined solely to the lateral segments of the brain stem at the level of the pons because cats, dogs, and monkeys in which the lateral segments were sectioned, leaving the medial segments intact (as indicated by the lesion for Cat 48-B), exhibited no detectable deviation from the normal in heat regulation either in the acute or chronic state.

#### *Transection of brain stem through caudal diencephalon*

*Acute experiments.* After carrying out the acute experiments described above, I endeavored to determine whether the mechanisms regulating heat production could be separated from the panting mechanisms at the level of the hypothalamus.<sup>2</sup> This seemed probable because the polypnea induced by light anaesthesia in normal animals had also been elicited in acute midbrain preparations.<sup>10</sup> In this study some 20 cats were maintained for 3 to 8 days following a complete transection which passed just anterior to the superior colliculi dorsally and through the mammillary bodies ventrally (indicated by line 1, Fig. 2). Without exception, such animals exhibited no ability to prevent a fall in their rectal temperature, it being necessary to house them in an incubator. When removed from the incubator and placed in an ordinary heated

room, their rectal temperatures fell rapidly to low levels and there was no shivering. All except two animals of this group also failed to pant even when overheated to the extent of convulsive prostration at rectal temperatures from 42.5° to 43.5°C. In two animals, however, typical panting was elicited by overheating with a heat beam. One such experiment on a cat is summarized in Table I. It will be noted that although panting was typical, with mouth open and tongue protruding, the maximal rate was slightly submaximal for the normal cat.

In an effort to determine whether transections at higher levels were less prone to eliminate the panting mechanism in the acute state, another series of some 30 cats was studied following transections at various levels of the diencephalon. It was found that when transections passed through the level of the chiasm ventrally (as indicated by lines 2 and 3 in Fig. 2) the animals usually were able to maintain normal rectal temperatures for 24-72 hours (shivering being present) after operation. Nevertheless, overheating these animals to fatal heat prostration failed in most instances to elicit panting. In the preparations in which panting did occur, its onset was definitely delayed until abnormally high rectal temperatures obtained. After its onset the panting was typical and maximal, however, and its abrupt onset was conspicuous.<sup>8</sup>

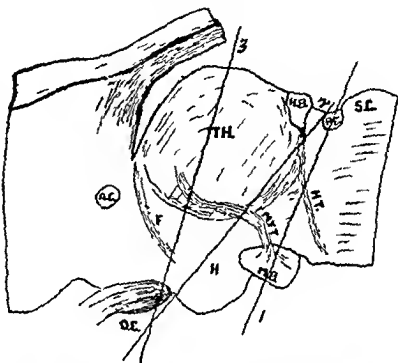


FIG 2 Drawing sketched from a sagittal section through the diencephalon of a dog. Lines 1, 2 and 3 indicate levels of transections in experiments described in the text. Compare with Fig 7a

Table I  
Cat 93—Operated upon Oct 23, 1929  
Observations—Oct 25

Time	Rectal temperature	Respiratory rate
9:10	38	22
11:30	38.2	30
11:34	Heat beam on animal	
11:37		60
11:40	39.0	90
11:59	39.8	130
12:05	40.7	150
12:13	Heat after water bath	170
12:16	42.5	150
12:27	41.3	90
2:05	36.5	90



*Chronic experiments.* The foregoing results on acute material suggested that the essential cephalic brain stem structures which regulate heat production are located rostral to the midbrain. However, the possibility remained that they might be located in part in the cephalic midbrain and only temporarily impaired by the acute lesion. (The failure to elicit panting in the majority of such preparations was interpreted on this basis.) If this were true, some heat regulatory power should return in chronic preparations of this kind. I had had little success in maintaining chronic midbrain animals, *i.e.*, 4 to 6 weeks after operation. Attention, therefore, was focussed upon postoperative care,<sup>6</sup> and specific heating and cooling tests were made only infrequently and for short periods. *It was found (verifying our observations on acute material) that maximal, typical panting is elicitable in the chronic midbrain cat and dog.* In some instances the rectal temperature threshold remained above normal, while in others panting began before any appreciable rise in temperature occurred. Following high transections in the cat, there appeared in the sub-acute and early chronic state (see protocol of Cat 10 below) some power to prevent a fall in rectal temperature when the animal was subjected to a cool environment.<sup>4</sup> Such a residual power was not present in the dog, at least to the extent seen in cats, following a transection at a corresponding level (see protocol of Dog 289).

Table II. Cat 10

Day after operation.	Rectal temperature.
	°C.
14th 9:00 A.M.	39.0 In incubator.
2:30 P.M.	39.2 In incubator.
	Put in refrigerated box.
2:55 P.M.	38.2 No shivering.
3:25 P.M.	36.5 No shivering.
4:45 P.M.	34.5 No shivering.
5:45 P.M.	31.5 No shivering.
	Removed from refrigerated box.
24th 7:00 A.M.	38.0 Room temperature 23°C.
9:40 A.M.	38.2
	Put in refrigerated box.
11:45 A.M.	36.0 No shivering.
2:00 P.M.	34.0 No shivering.

*CAT 10—Operation, Oct. 11, 1932.* Complete transection of the brain stem through the cephalic level of the midbrain was attempted through a bilateral dorsal exposure. The lesion was placed by traction with a milliner's needle. Immediately following operation this preparation failed to maintain a normal rectal temperature in the presence of a cool environment and had to be kept in a warm incubator. After 2 weeks it demonstrated considerable power of heat maintenance and could be housed in an unheated cage. Table II shows, however, that it remained unable normally to combat a cool environment. On the 9th day after operation, typical, vigorous, maximal panting was elicited when put in a heated box; its rectal temperature was 41.9°C. and panting appeared abruptly as in other preparations. It was not removed from the heated box until its rectal temperature had reached 43°C.; no sweat appeared on the toe pads, although panting continued uninterrupted. The preparation was again placed in the heated box on the 45th day after operation; at a rectal temperature of 41°C. the respiratory rate was only 66 per min. and 30 minutes later the cat was panting vigorously, the rectal temperature being then 43.8°C. The preparation was then cooled by immersion; exitus occurred the following day.

Sections through the lesion demonstrated that the transection was complete at the

level of the posterior commissure dorsally and the mammillary body ventrally except for a small tag of dorsal tissue on the left side into which the posterior commissure ended (Figs. 3a and b).

**DOG 289—Operation, Apr. 17, 1934.** Complete transection of the brain stem through the cephalic level of the midbrain was attempted via a bilateral dorsal exposure. Following operation this dog failed to maintain its rectal temperature which was 28.5°, 29.2°, 30° and 28.5°C. on the 1st, 3rd, 12th, 18th, and 28th days after operation respectively. It was necessary to house this dog in an incubator during its entire postoperative course. Shivering was never observed. The dog was tested for panting on the 28th day after operation. At this time typical panting at a relatively slow rate (105 per min.) was elicited in an incubator when the animal's rectal temperature was 38°C. The dog was removed from the heated box and respiration continued at a rapid rate for some time in spite of a fall in the rectal temperature. On this same day it was placed outside in the sun. Typical rapid panting ensued, at a rectal temperature of 38.2°C. The following morning the dog began vomiting spontaneously and was sacrificed. The location and extent of the lesion is shown in Fig. 3. e-h.



FIG. 3. a-d are photomicrographs of cross sections from the series on Cat 10. Note completeness of transection except for dorsal medial tag on left side. e-h are photomicrographs of cross sections from the series on Dog 289. Note completeness of transection.

*Isolation of the hypothalamus*

*Acute experiments.* The elimination of the mechanisms regulating heat production with sparing of the panting mechanism was particularly well demonstrated in acute preparations in which the hypothalamus was either completely isolated by a narrow lesion from the rest of the brain stem or its dorso-caudal connections were severed.<sup>3</sup> In certain of these preparations vigorous, typical panting was readily elicited in spite of the animals' being in a cool environment with a normal or even an extreme subnormal rectal temperature. Stimuli which normally are not concerned with, or at least are not adequate to excite, panting elicited polypnea with ease. Thus movements of the animal, passive or spontaneous, such as: arousal from sleep, urination or defecation, massage so slight as pinching the tail, activated the polypnea mechanism. In addition, *these preparations exhibited continuous visible dilatation of the ear vessels.* The following briefs from protocols are representative.

*CAT 61—Operation, Feb. 8, 1932.* An attempt was made to sever the hypothalamus from the lower brain stem by "over-cutting" its caudal, dorsal, and cephalic connections with a small blunt probe. No surface bleeding occurred.

*Postoperative notes.* The cat's temperature was maintained near normal in an incubator at 30°C. for the first 3 days after operation. On the 3rd evening the incubator was cooled to 24°C. The following morning the cat's rectal temperature was 28°C. There was no shivering. On the 5th morning the rectal temperature was 31°C., with the incubator at 27°C. There was again no shivering. Respiration at this time was fast, and pneumonia was suspected; the blood vessels of the ears were dilated. On the 8th day respiratory rate of the undisturbed animal was 36 per min. and rectal temperature 34°C.; when picked up it promptly began typical panting. The ear vessels were again dilated. On the 11th day, pneumonia not having developed, the animal's reaction to overheating was tested. At 1:30 p.m. it was placed in an incubator at 35°C. Its rectal temperature was 34.4°C. and its respiratory rate was 100 per min., when typical panting was present after handling. At 1:45 p.m. the cat had become quieter in the incubator and was breathing 75 times per min. At 2:00 p.m. respiration was 130 per min., the mouth was not open, *i.e.*, panting was not yet present. At 2:10 the cat was panting vigorously and typically, the mouth being open and the tongue protruding. The respiratory rate was over 180 per min. and rectal temperature 39.2°C. The cat had not gotten to its feet or moved except to stretch; *panting in this instance was, therefore, elicited normally by heating.* At 2:35 the rectal temperature was 41°C. and the cat was still panting vigorously. On the 13th day temperature was 32.5°C. with no shivering; at 7 p.m. on this day the preparation was found dead.

At autopsy the lungs were normal. The brain was clean and after the pia was stripped the lesion was readily seen (Fig. 4) to pass well ahead of the optic chiasm anteriorly and through the anterior extent of the mammillary bodies caudally. Serial sections of this region revealed that the dorsal extent of the lesion encroached slightly upon the ventral portion of the thalamus. The whole of the hypothalamus except in its most caudal extent (caudal half of the mammillary bodies), was completely separated from the lower brain stem. The separated tissue still maintained its blood supply since there was no softening evident; likewise there were no thalamic infarcts.

*CAT 111—Operation, May 18, 1932.* The hypothalamus was isolated as in Cat 61, after which it was macerated with forceps.



FIG. 4. Photograph of the brain of Cat 61 showing the surface boundaries of the lesion. Note that the hypothalamus is isolated from surrounding tissue. Also, that the isolated hypothalamic tissue exhibits no softening.

*Postoperative notes* The morning after operation, respiration was rapid, being 108 per min when the cat was resting. The ear vessels were markedly dilated, and massaging did not elicit panting. On the 2nd postoperative day the respiratory rate was 150 when the cat was resting in an incubator at 27°C and rectal temperature 36°C. The ear vessels were dilated and massage of the animal elicited typical panting. On the 3rd morning the cat was panting typically with a rectal temperature of 37°C, being housed in an incubator at 31°C. The cat was sacrificed on this day by administration of nembutal. The lungs were normal and the brain clean except for subpial blood stains on the right temporal pole. The region of macerated hypothalamus was filled with clotted blood (Fig 5). There were no thalamic infarcts.

*CAT 112—Operation May 6 1932* The hypothalamus was first isolated from its dorso caudal connections and then the hypothalamic tissue was macerated with forceps. No hemorrhage occurred.

*Postoperative notes* The morning after operation the cat's rectal temperature was 28°C and on the 5th morning 30°C. There was no shivering. At rest its respiratory rate was 150 per min, but the mouth was not open in the panting attitude. As the cat stood up and began urinating it suddenly began panting vigorously and typically. The ear vessels were moderately dilated. The cat subsequently until death on the 8th day, maintained a constant picture. It exhibited no evidence of being able to maintain its rectal temperature or to shiver. The ear vessels were continually dilated. Respiration continued rapid even when resting, typical panting always occurred when the animal was handled or moved spontaneously. The whole of the hypothalamus was involved by anemic necrosis without infringement upon the thalamus, except the most ventral portion (Fig 6).

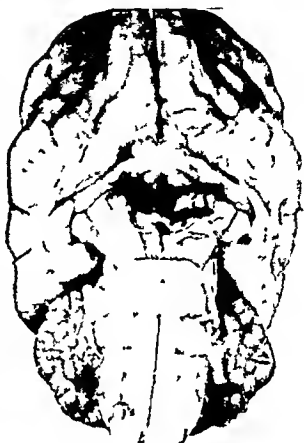


FIG 5 Photograph of the brain of Cat 111. Note the absence of the hypothalamus and its replacement with clotted blood.



FIG 6 Photograph of a cross section at the level of the hypothalamus from the series on Cat 112. Note the entire hypothalamus is involved by anemic necrosis.

*Chronic experiments* A persistent absence of the mechanisms regulating heat production with a sparing of those regulating heat loss has been encountered in several dogs, maintained to chronicity, in which the dorso caudal connections of the hypothalamic grey were severed. Such dogs in the acute state exhibited an inability to regulate against a lowered environmental temperature, but in the chronic state some residual thermogenic power was evident. Thus, sev-

tendency to polypnea. Subsequent to the test, however, it exhibited a definitely increased tendency to pant; thus, on the 25th day vigorous panting occurred with a rectal temperature of 35°C. and again on the 27th day with a rectal temperature of 34°C. On both occasions the humidity of the room was high and the dog was walking around. It is not clear, therefore, whether panting in these instances was due to an increased susceptibility to heat or a result of activity, as in Dog 116. It was suspected that the latter was the case. In any event, the animal became more sensitive after its experience on the 21st day.

Death occurred on the 30th day from a jaw infection. The lungs and trachea were clean. The experimental lesion passed just dorsal and caudal to the caudodorsal and caudal extent of the mammillo-thalamic tracts and was like that in Dog 116, except that it did not reach as far anteriorly and dorsally. There was also a sizable anemic infarct in the thalamus on the right side (Fig. 7).

Dogs in which the lesions fell short of isolating the whole of the hypothalamic grey exhibited normal power of regulating its heat production in the chronic state. Lesions of this type are shown in Fig. 8. The photomicrograph shown in Fig. 8a is of a section from the series on Dog 102-C. This dog was operated upon in April, 1936, and sacrificed three months later. The line in Fig. 8b indicates the dorso-caudal borders of the lesion in Dog 398-B, operated upon in July 1934, and surviving three months. Most of the hypothalamic grey anterior and ventral to the black line was involved by lesion scar. These dogs, as is typical following such lesions, ran slightly subnormal rectal temperatures for several days after operation but subsequently exhibited no deviation from the normal either when subjected to low (refrigerated box at 5°C.) or high (out-of-doors in summer at 30–35°C.) environmental temperatures.

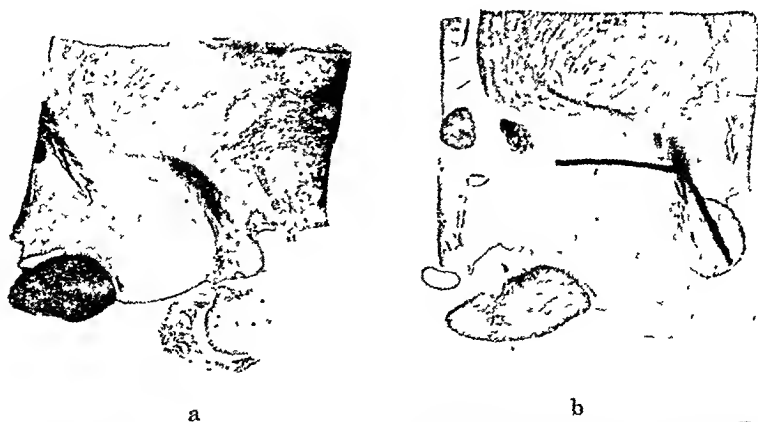


FIG. 8a. Photomicrograph of a sagittal section from the series on Dog 102-C. Note that the lesion passed just anterior to the mammillo-thalamic tract, and did not reach through the uppermost extent of the hypothalamus. b. A sagittal section through the hypothalamus with the dorso-caudal extent of the lesion in Dog 398-B indicated by an inked line.

## DISCUSSION

The permanent impairment of the mechanisms regulating heat production, caused by wide, medial transverse lesions at the upper level of the pons (Dog 315), is probably to be interpreted as due to the severance of descending fibers

normally essential to this function.\* If this is correct, it is evident that these fibers (descending from neuralelements located in the posterior hypothalamus) have a wide-spread distribution at the level of the pons. This is in general agreement with conclusions drawn by Magoun, Ranson and Hetherington.<sup>11</sup> The ability to maintain a normal rectal temperature and to shiver when subjected to a cool environment was not eliminated by medial transverse lesions until they reached well laterally (Cat 39) nor by lateral transverse lesions on both sides so long as strips of medial tissue remained unsevered (Cat 48). Shivering is, however, eliminated by medial transverse lesions before elimination of the mechanisms of metabolic heat liberation, indicating more lateral distribution of the latter fibers. The experiments do not give information regarding the relative density of fibers in a pontile cross-section, since nothing is known regarding the number that can be destroyed without showing a deficit in function. The experiments do demonstrate, as would be expected, that there is an enormous reserve in this respect. It is quite possible, therefore, that the fibers subserving the mechanisms of heat production are actually more numerous medially than they are laterally, as Beattie, Brow and Long<sup>12</sup> found for fiber degeneration following posterior hypothalamic lesions. It is likewise evident that the fibers descending from the cephalic mechanisms controlling heat loss also have a wide distribution at the level of the pons, since the power to prevent a rise in body temperature is not eliminated either by extensive bilateral medial or lateral transverse section. Our evidence indicates that the power to prevent a rise in rectal temperature is impaired before the power to prevent a fall when lateral lesions infringe upon the medial reticular areas. This suggests that the heat loss fibers are sparse in the tissue immediately adjacent to the midline, at the level of the pons. Peet and List,<sup>13</sup> on the basis of clinical material, suspect that the descending fibers controlling sweat secretion also have a lateral course at this level.

The failure of chronic midbrain cats and, especially dogs, as well as animals with dorso-caudal hypothalamic connections severed, to regulate adequately against a fall in body temperature indicates that the bulk of the essential cephalic neural elements are actually confined to the hypothalamus in these species. Cat 10 (high midbrain) in the chronic state possessed considerable power to prevent a fall in rectal temperature when subjected to low environmental temperatures.<sup>4</sup> Thauer and Peters<sup>14</sup> have shown this to be true, possibly to a more marked degree, in the rabbit, although Cat 10 is essentially identical to Rabbit 89 of their series. To a lesser extent, dogs in which only that portion of the hypothalamus caudal to the mammillo-thalamic tracts remained connected with the midbrain (Dogs 116 and 117) also maintained their rectal temperature. Since the midbrain dog (Dog 289) failed to display this residual power, it may be that a progressive encephalization of these

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\* It is recognized that at times the rectal temperature is maintained in varying degrees, with frequent uncontrollable hyperthermias, following complete transection of the brain stem at the level of the pons in the cat (Keller, A. D. and Hare, W. K., *Proc. Soc. exp. Biol. N. Y.*, 1932, 29: 1167) and dog. It has not yet been determined whether this is due to a release of subsidiary mechanisms or to an abortive stimulatory effect.

elements occurs in the rabbit, cat, and dog. In any event, the question arises whether this residual power of heat maintenance is due to the recovery, during the subacute state, of cells caudal to the lesion normally concerned with this function or to the released activity of lower subsidiary mechanisms. The first alternative seems the most probable.

On the basis of acute experiments, I am in agreement with Bazett, Alpers, and Erb<sup>7</sup> and Teague and Ranson<sup>8</sup> that the anterior hypothalamus is not essential for the adequate regulation of body temperature against low environmental temperature. Furthermore, the ventral two-thirds of the hypothalamic grey can be separated or destroyed in the dog and cat (Dog 398: Fig. 8) without permanently eliminating this mechanism.<sup>4</sup> The elicitation of typical thermal *panting* in acute midbrain preparations as well as in animals with the hypothalamic connections severed demonstrates that the hypothalamus is not essential to this function. Further, since such preparations in the chronic state possess the ability of preventing a rise in body temperature, it is evident that this function in these circumstance is likewise independent of the hypothalamus. Whether or not avenues of heat loss other than those of panting and vasodilation were utilized in attaining this end is not yet clear. Visible sweat was not observed in these preparations. The recent work of Ranson, Fisher, and Ingram<sup>9</sup> suggests that the cephalic representation of the sweat glands is confined to the hypothalamus in the monkey. This may likewise be true in the dog and cat. In this connection, it is to be borne in mind that the work of Hasama<sup>1</sup> and Magoun, Harrison, Brobeck and Ranson<sup>15</sup> make it seem certain that the cephalic (brain stem) representation of the mechanisms controlling heat loss extends upward into the hypothalamus.

The fact that the mechanism regulating heat loss carries on adequately in preparations in which the mechanisms controlling heat production have been virtually eliminated, bears ample evidence of functional *independence* of the former from the latter. In spite of this, a reciprocal innervation between the two mechanisms is to be expected. The striking release of the panting and vasodilator outflows in certain of the anhypothalamic and midbrain preparations may be evidence of such a relationship. It is more specifically shown in preparations in which thermal panting was elicited only when the rectal temperature reached the normal panting level, yet continued for some time after the rectal temperature was again reduced below normal (see protocols of Dog 289 and Cat 61). Thus, in these preparations the mechanism for activating the heat loss outflows is essentially normal, but that for arresting their activity is partially impaired. Whether or not the increased susceptibility to panting at low rectal and environmental temperatures is a result of the absence of a normal reciprocal innervation between the two mechanisms, this phenomenon must be due to some sort of released activity because it continues into the chronic state. An irritative effect would be present only in the acute and subacute states. This increased susceptibility to polypnea encountered in our preparations (1932) is undoubtedly the same phenomenon described by Lilienthal and Otenasek<sup>16</sup> and termed by them "decorticate polypneic panting" (1937).

## SUMMARY

In the cat and the dog the mechanisms controlling heat production can be virtually eliminated, while sparing the mechanisms regulating heat loss, by the following procedures (i) severing all descending fibers except those in the outer extent of the lateral reticular formations by a wide medial transverse lesion at the upper pontine level, (ii) complete transection of the brain stem through the caudal extent of the diencephalon, and (iii) severing the dorso-caudal hypothalamic connections

The structural elements subserving the mechanisms of heat loss and heat production in the *cephalic brain stem* have separate anatomical loci, the former extending further caudally than does the latter. Further, the fibers descending from the mechanisms controlling heat loss have a slightly greater lateral distribution at the level of the pons than do those involved in heat production. Both sets of fibers are widely distributed at this level.

Although activation of the heat loss and the heat production mechanisms is quite independent, a reciprocal innervation, nevertheless, exists between the two.

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## ANOXIA AND BRAIN POTENTIALS

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MANY METHODS for determining the absolute and relative oxygen requirements of different parts of the nervous system depend on recognition of structural or functional changes which follow deprivation of the normal oxygen supply. Since it is generally believed that the structures with the highest respiratory rates suffer most rapidly from oxygen want, three *time* parameters can be used to obtain quantitative evidence of relative oxygen requirements (Gerard, 1938a, b); (i) survival time, *i.e.*, the duration of anoxia required to bring about the change in question (*e.g.*, loss of response, histologic alteration); (ii) revival time, *i.e.*, the duration of anoxia which still permits reversal of this change when oxygen is restored; and (iii) recovery time, *i.e.*, the interval between readmission of oxygen and start of restoration to normal.

Anoxia of the brain *in situ* may be produced suddenly by quick occlusion of arterial blood flow. Using rabbits, Astley Cooper, in 1836, first blocked both carotids and vertebrals, and observed muscle spasm and respiratory failure, and similar though milder changes in dogs (because of their richer anastomoses). This work has been extended to other animals (Hill, 1900; Pike, Guthrie and Stewart, 1908a; Gildea and Cobb, 1930), and to the resuscitation of the head and brain by perfusion of the isolated head (Hayem and Barrier, 1887; Pike, Guthrie and Stewart, 1908b; Crile and Dolley, 1906; Heymans, Jourdan, and Nowak, 1934); and anaemic decerebration has been introduced (Pollock and Davis, 1923; Swenson, 1925; Kabat and Dennis, 1938). The differential effects of anoxia have been investigated further by studying, during or after anemia, histological changes (Gomez and Pike, 1909; Gildea and Cobb, 1930), conditioned reflexes (Andrejev, 1935,a,b), reflexes of the brain stem (Heymans and coworkers, 1934, 1935, 1937), and changes in chronaxie (Rizzolo, 1927; Richard, 1936; A. and B. Chauchard, 1936). Of these methods, only the histological approach lends itself to fine localization and even this is unsuccessful when applied to the brains of animals dying during, or soon after, acute anaemia (Gomez and Pike, 1909).

The newer electrical techniques offer a better means of following continuously the influence of anoxia on specific brain regions. Prawdicz-Neminski (1925) obtained waves of 11 to 16 per sec. from the motor and visual cortices of curarised dogs, with the string galvanometer, and followed changes in them after suspending artificial respiration. The potentials did not alter during the (estimated) dyspnoea phase of asphyxia; they increased through the convulsive phase but reached a maximum, at 3 minutes, after convulsions ceased, and finally disappeared in 5 minutes, though the heart continued to beat. This refuted the contention (Tchiriev, 1904) that brain potentials were due to movement of blood and lymph. Bartley and Bishop (1933) reported a periodic

paling and flushing of the cortex associated with a decrease and increase of potentials, and a complete absence of potentials 3 to 5 minutes after ligating a superficial artery supplying the area under observation. Bilateral carotid occlusion abolished the 8 to 18 per sec potentials from the cat's motor cortex in 20 sec (Simpson and Derbyshire, 1934). One of their records (in Gibbs, Davis, and Lennox, 1935) shows return in 30 secs after release of a 60 sec occlusion. The occipital cortex showed less change, attributed to circulation through the vertebrals.

The human EEG was reported (Berger, 1934) to become more regular and with larger waves, rather suddenly, after about seven minutes rebreathing from a closed bag with CO<sub>2</sub> absorbed. Breathing mixtures of low oxygen pressure slows and diminishes the 10 per sec waves in man (Davis, Davis, and Thompson, 1938) leading ultimately to loss of all activity or appearance of the slow "delta" waves. Potentials of the "isolated" cat brain (severed at the pons, Bremer, 1935) are affected in 12 secs after ceasing artificial respiration and gone in 40 to 50 secs (suprasylvian gyrus, Bremer and Thomas, 1936), to reappear within 3 secs (Bremer and Thomas, 1936, Fig 1E) after respiration is resumed. Thalamic potentials are lost in 60 secs following simple carotid occlusion (Dubner, unpublished). A sufficient fall in blood pressure, produced by raised pericardial pressure (Beecher, McDonough, and Forbes, 1938) or by peripheral vagus stimulation (Bailey and Bremer, 1938), likewise eliminates cortical potentials in the cat.

In many of the studies cited, anoxia has been far from complete, due to continued vertebral and other circulation, and times from interference with respiration or oxygen supply to changes in brain potentials do not, of course, give the survival time for brain structures but this plus an unknown duration of diminishing oxygen delivery to them. Further, no comparative values for various brain structures are available. It was our intention, therefore, to obtain records of potentials from a number of regions and to follow quantitatively the changes induced in them by abrupt and complete stoppage or release of the blood flow, in the hope that these survival and recovery times could be related to other data indicating the relative respiratory requirements of brain structures.

#### METHOD

Cats were anaesthetised with nembutal (30 mg per kg intraperitoneally), a tracheal cannula inserted, lifting ligatures placed on both carotids and the vertebrals exposed and ligated. In the cat, complete interruption of the carotid and vertebral circulations (verified at autopsy) leads to respiratory failure in 30-40 secs, preceded by variable tonic and clonic contractions and such failure after occluding the carotids temporarily was taken as an indication of the successful elimination of all vertebral flow. The control is important for accessory vertebrals are common especially on the left side, and as many as three vessels on one side and two on the other have been encountered in three animals. Sometimes it was necessary to ligate the vertebrals at their origins after dissecting along the subclavians usually exposure between the longus colli muscle and the 7th and 8th cervical roots was sufficient.

The animal was now turned over, the head elevated, and extensive removal of the left side of the calvarium achieved with relatively little bleeding. The Horsley Clarke instrument was then attached. Concentric or bipolar leads fed potentials through a push

pull, resistance-capacity coupled amplifier into a crystograph, loud speaker, and cathode ray oscillograph. Two channels were usually used, a lead from the motor cortex serving as a standard of reference for another one which was moved about at intervals. The cortex was carefully kept warm and moist with ringer-soaked cotton and the scalp wound was closed with clips between adjustments of electrodes.

Finally, the right (contralateral) carotid was ligated, and the thread about the left one led into a glass tube so that it could be occluded by traction without otherwise disturbing the animal or producing an electrical artifact. Anaemia periods of 20–180 secs. were used, usually not repeated within ten minutes of a preceding one. Observations began three to four hours after anaesthesia was induced and when the anaesthetic effect had largely worn off. When repeated anoxia had modified the preparation too much, after several hours, the head was perfused with Ringer followed by 10 per cent formalin, and allowed to harden. The electrode positions were checked by gross section, the needle track being well marked and its deepest point taken. Agreement with the Horsley-Clarke coordinates (Gerard, Marshall, and Saul, 1936) was usually good.

### RESULTS

Satisfactory experiments were performed on 15 cats, with many observations from each of several regions. The usual signs of brain anaemia were regularly observed: first increased respiration (usually immediate in onset) followed by general tonic and clonic movements (from the 20th to the 60th sec.), then progressively diminishing breathing and movements ending in apnoea and flaccid areflexia (30 to 40 secs. for cessation of respiration; 60 to 70 for passive posture). A comparable sequence is manifest in brain potentials, which will be described first as typical of the motor cortex. Special variations will be considered later.

In the motor cortex (Fig. 1), high frequency waves appear or increase in speed and amplitude from one or two seconds after cessation of respiration until 10 or more. By 12 secs. all fast waves have disappeared, and the slower ones (1 to 3 per sec.) by 20. The record remains flat for the remainder of a 29-second anaemia period. Five seconds after restoring blood flow, electrical activity is ushered in by low irregular waves, with a spindle of 6 to 9 per sec. starting at the ninth second and lasting nine more, gradually fading into a new abruptly starting spindle of considerable regularity. Fast waves soon appear, and are partly superimposed on other spindles, which continue to reappear with diminishing amplitude and regularity and with increasing wave frequency (10 to 12 per sec.) and longer intervals between groups until, by four to six minutes, the normal appearance of continuous rapid waves or rapid waves and spindles is established.

The post-anaemic spindles are especially characteristic and also vary most consistently with the duration of the anaemia period. With longer occlusion, the spindles begin later after release and are individually longer (compare the values for a 235 sec. occlusion with those above for a 29 sec. one: the first spindle began 33 sec. after release and continued for 40 sec., instead of 9 and 9). In fact, as shown in Fig. 2, there seems to be a linear relation between occlusion time and recovery time. Furthermore, the spindles usually start at slow frequencies and finish with rapid ones (variations from 6 per sec. to 12 per sec. have been found between the beginning and the end of long spindles). These relatively slow waves follow anaemia even though fast waves only were

discernible in the preocclusion record; when the preocclusion record contains spindles, these are usually smaller than the postocclusion ones. (This enhancement of existing rhythms has been found also in the geniculate body and the cerebellar grey.) The beginning and ending of spindles may be gradual or abrupt: usually the first postanaemic one has a gradual start, while the ones which follow become increasingly abrupt (Fig. 3).

Fast potentials, throughout the brain, are more susceptible to anaemia than slow ones. After an initial increase, they disappear before the slow; they return later when circulation is restored; and they are abolished irreversibly after repeated anoxia periods when the slow waves may show no measurable modifications. Slow waves from the medulla and cerebellum are so resistant to anaemia that they often remained at the end of an occlusion lasting two to three minutes, although the fast oscillations were gone in 40 or 10 secs., respectively. Bursts of rapid waves often appeared late in these regions, however, and might be seen for 4 to 6 sec. periods as late as one minute after occlusion. The possibility that these variations might be due to incomplete anaemia could not be directly attacked, but the criteria of anaemia were satisfied in these animals (including the disappearance of simultaneously recorded potentials from the motor cortex, and the complete disappearance of potentials from other regions in the medulla and cerebellum).

The obex region of the medulla has commonly developed a special

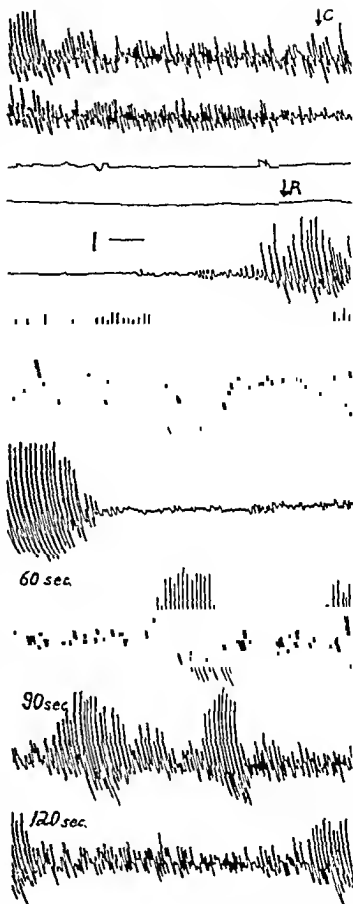


FIG. 1. Anoxia and recovery of motor cortex. First 7 strips continuous (70 secs.), lower 3 at indicated times after release. Carotid clamped at first arrow (C) released at second (R). In all figures, horizontal ruled line is 1 second and vertical is 100 microvolts. Read from left to right.

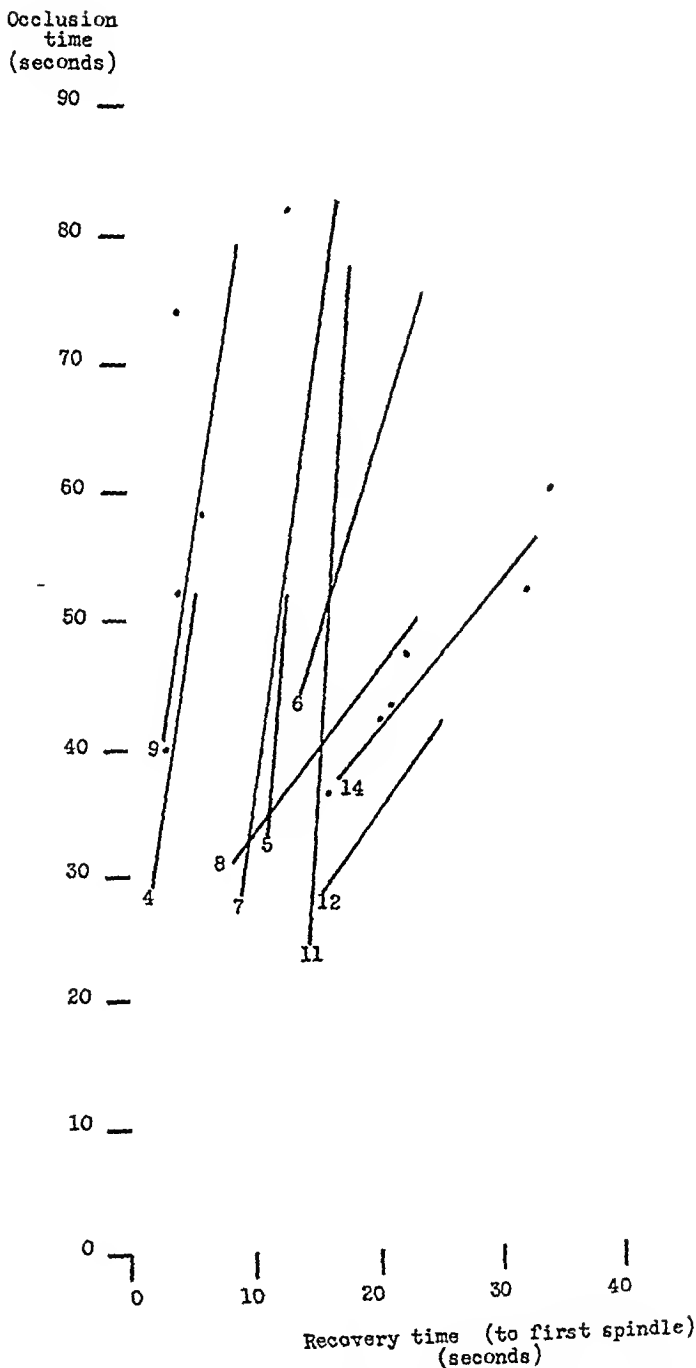


FIG. 2. Duration of recovery time as a function of duration of occlusion. The data indicate a linear relationship. The curves for individual animals seem to fall into two groups of different slope. Data for motor cortex, on nine cats (each one line). Observed points shown for cats 9 and 14; others (73 points) omitted. One aberrant animal not shown.

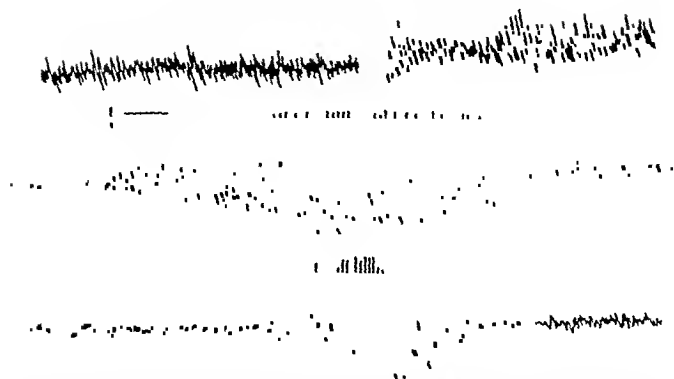


FIG 3 Motor cortex. Upper left, before anoxia; upper right, 4½ minutes after release, amplitude still increased. Middle and bottom records, continuous strip from 10 to 40 seconds after release of a 30 second occlusion. Note gradual (first) and abrupt (second) start and end of spindles, also duration, regularity, amplitude and accelerating frequency in each.

and striking slow potential wave; appearing suddenly after the initially present waves have become flattened out, increasing to large amplitudes (60 microvolts from a previous level of about 20) during continued occlusion, and persisting for a minute or more into the post-anaemic period. These potentials start out coincident with the heart beat, but the individual wave, initially of rough sine form, is far longer and slower than any electrocardiogram element (Fig. 4), and as it grows in amplitude, a notch, or even two successively, ap-

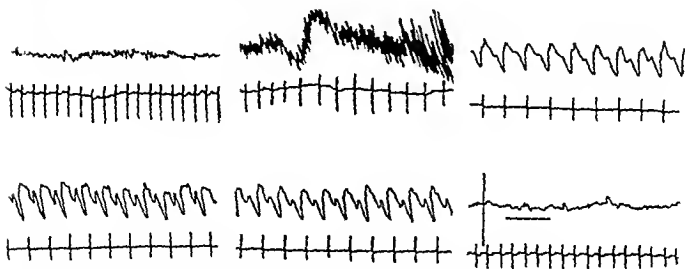


FIG 4 Medulla, below obex (above) and electrocardiogram (below). Upper row, left to right: before occlusion, 5 secs, and 45 secs after occlusion. Lower row, 70 secs and 150 secs after occlusion, and 45 secs after release. Note high frequency waves early in occlusion followed by slow waves in time with heart beat.

pears on it. The absence of large arteries from this region, and the peculiar shape of the wave make it unlikely that this could be an arterial artifact (all the more so because the blood supply is clamped off); but it is much more probable that it is an artifact from the venous pulse, caused by movements of blood in the large posterior spinal vein nearby. Evoked potentials, from shining light in the eyes, as well as the spontaneous ones, were studied in the lateral geniculate body in relation to anaemia. The spontaneous waves, and the "on" and "off" discharges disappeared together after about 35 secs. of occlusion, and returned together following release.

Since our main interest in these experiments was to obtain survival times as an indication of the respiratory requirements of various brain masses, it was important to determine to what extent the anaemia acts via anoxia. Interruption of the blood supply causes a fall in available oxygen and glucose (of prime importance to brain) and a rise in  $\text{CO}_2$  and other acids. Altered salt distribution is secondary to anoxia (Dennis and Mullin, 1938; Tupikova and Gerard, unpubl.) and changes in other substances are probably of lesser im-

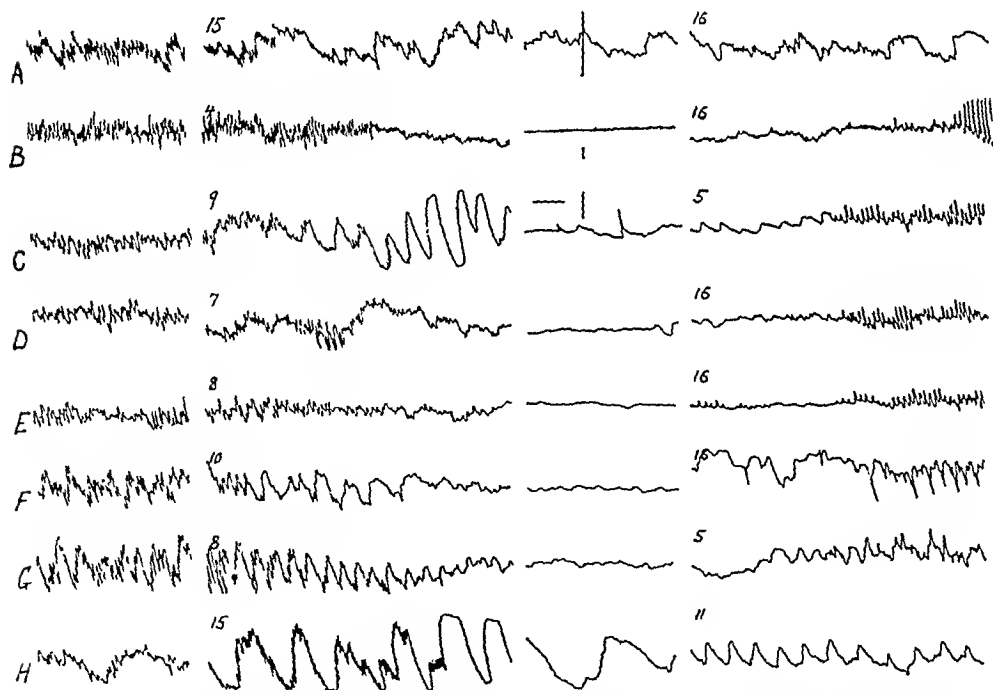


FIG. 5. Characteristic records from various brain regions. The first vertical column contains 5 sec. strips before occlusion; in the second column each strip is 10 secs. beginning at the indicated number of seconds after occlusion; the 5 sec. strips in the third column are from the 40th to the 45th sec. of a 50 to 70 sec. total occlusion period; the 10 sec. strips in the fourth column begin at the indicated number of seconds after release. The horizontal rows are from the following structures: A, cerebellar cortex; B, motor cortex; C, fascia dentata; D, lateral nucleus of the thalamus; E, dorsal nucleus of the thalamus; F, medial geniculate body; G, lateral geniculate body; H, spinal Vth tract in medulla. Note different amplifications for rows A and B; from C on all alike.

portance. Carbon dioxide accumulation has been shown to increase fast waves (Lennox, Gibbs, and Gibbs, 1938) and may contribute to the augmented high frequency potentials encountered early in anoxia. In sufficient excess,  $\text{CO}_2$  also abolishes activity (Bremer and Thomas, 1936; Lennox, Gibbs, and Gibbs, 1936; Gerard, Marshall, and Saul, 1936). Hypoglycaemia acts much like (Gellhorn, Ingraham, and Moldavsky, 1938) and even directly induces (Himwich, *et al.*, 1938) a lowered oxygen usage, so it was especially important to evaluate this factor in anaemia.

If sugar depletion were the primary cause of the potential changes of anaemia, then increasing the blood sugar before occlusion should delay the potential changes. This was not the case: intravenous glucose up to two grams per kilo, administered just before occlusion, had no effect on the time relations or the changes seen. Lowered blood sugar (insulin, three units/kilo, one hour before occlusion), however, did alter the effects of anaemia. The early increase in rapid waves (and motor discharges) is advanced and augmented, total activity is lost sooner—*e.g.*, 23 instead of 33 sec in the geniculate—and the post-occlusion spindles are delayed and less regular. Further, a large (30–50  $\mu\text{V}$ ), slow (0.7 sec.) wave with abrupt polarity changes appeared late in the anaemia period, after the base line had become flat, simultaneously in motor cortex and geniculate. It is likely that this wave is of the same nature as the slow waves occasionally seen after occlusion in other records, simultaneously in different parts of the brain which have not been showing synchrony, and represents blood movements.

Apart from occlusion, an interesting effect of anoxia was brought out by the insulin action, which initiated Cheyne-Stokes respiration. During the apnoeic intervals, cortical potentials showed spindles which faded to quiescence; with the resumption of respiration, the spindles returned, and activity was maximal as the respiration reached its peak. It seems probable, then, that anaemia acts mainly via anoxia if the blood sugar is not too low at the start;

Table I  
Survival Times

Cephalic region	Time for disappearance of potentials (seconds)
Cerebellar grey	10–12
Ammon's horn	10–12
Cerebral grey (cortex)	14–15
Subcortical white matter	20–22
Corona radiata	20–25
Caudate nucleus	25–27
Ventrolateral nucleus of thalamus	28–33
Lateral geniculate body	32–37
Medulla	30–40
Reticular formation near n. vagus	over 2 mins
tuberculum cuneatum	over 2 mins
spinal V tract	over 2 mins

Times given are for representative occlusions performed at the beginning of experimentation; successive occlusions lower these values from 1 to 5 secs.



and the different survival and revival times for particular regions are related to their oxygen needs. These times are shown in Tables I and II.

*Table II*  
Recovery Times

Cephalic region	Time from release of occluded carotid to beginning of restoration of normal waves (seconds)
Corona radiata	4-6
Dorsal nucleus of thalamus	6-8
Rubrospinal tract	10
Optic tract	10
Lateral geniculate	12-14
Fascia dentata	12-15
Lateral nucleus of thalamus	15-17
Cerebral cortex	17-19
Cerebellar grey	23-25

Times given are for 55-79 second occlusions brought to one minute by comparison with simultaneously recorded motor cortex records. Because of the variations from cat to cat (see Fig. 2), the above, typical, values have been taken from one animal.

Though particular structures have their individual time and form characteristics for loss and return of potentials (Fig. 5), certain wave trains not uncommonly return simultaneously in several regions. In such cases, after anaemia, bursts appear together, repeated or with increasing asynchrony (Fig. 6). The motor cortex has at one time or another shown such synchrony with: the lateral nucleus of the thalamus, the lateral geniculate body, the corona radiata, the cerebellar grey, and the caudate nucleus (where, as in Fig. 7, the synchrony is much better after anoxia than before).

### DISCUSSION

That anoxia alone can abolish brain potentials is clear from experiments on breathing mixtures of low oxygen pressure by man (Davis, Davis, and Thompson, 1938; Gibbs and Davis, 1935; Hoagland, 1938), and cats (Derbyshire, Rempel, Forbes, and Lambert, 1936), as well as from the present evidence. The changes which follow sudden anaemia are primarily due to anoxia, but hypoglycaemia and especially hypercapnia may well contribute, as also may the increased extracellular potassium induced by anoxia (Tupikova and Gerard, unpubl.; Dubner, 1938; Libet and Gerard, 1938). We have not specifically eliminated possible effects of afferent impulses from the carotid body, following sudden occlusion of the common carotid, but there is no reason to suspect that these might evoke the changes seen, nor do so with specific time differences from one brain region to another.

The possibility must be considered that the differential survival times found are a result of incomplete anaemia, those regions receiving the most blood naturally surviving the best. The only source of a continued blood supply would be the anterior spinal artery, which was not specifically ligated.

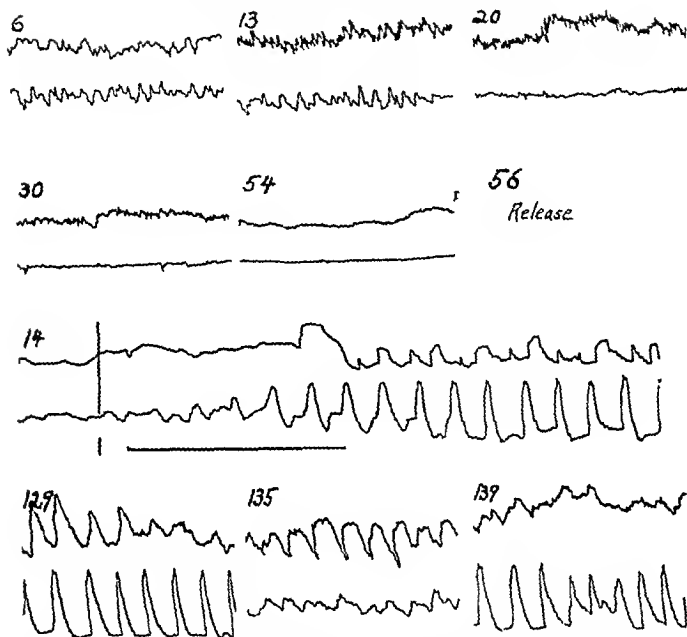


FIG 6 Cerebellar (upper) and motor (lower) cortex records, faster speed. Note the greater amplification for the cerebellar records. Upper two rows, at indicated second after occlusion, lower two rows, same after release. Note high frequency waves in cerebellum are much increased during anoxia when motor cortex has already become quiescent. After anoxia, note marked synchronization of cerebrum and cerebellum but also, within a few seconds of one another, completely independent rhythms in either one of these structures.

This is normally very small in the cat and, in the neck region, derives its blood mainly from the vertebral arteries above the level of their ligation. The respiratory center lies in the base of the medulla in the direct path of any blood still passing in the spinal artery; yet in all cases in which the four large arteries are ligated (and not in those in which even a branch of an accessory vertebral escaped) respiration failed in 28-35 seconds after occlusion. Further, it has been shown (Stewart, Guthrie, Burns, and Pike, 1906) that in similar preparations, pigment injected intravenously into the peripheral circulation usually did not reach above C3 or C4 and never above the calamus. Yet under these conditions potentials from the cerebellum have persisted after medullary activity was abolished. It seems, therefore, that a continued circulation of small amounts of blood can have little if any influence on the present results.

The survival times of particular brain regions may than be taken as an index of their relative respiration rates. That these have been significantly altered by anaesthesia is improbable. Nembutal is a short-acting barbiturate and several hours elapsed between its administration and the start of observations; and, even at an earlier stage, this drug has little influence on brain potentials (Bremer, 1936; Derbyshire, Rempel, Forbes, and Lambert, 1936; Beecher, McDonough, and Forbes, 1938). Also, the unanaesthetised isolated

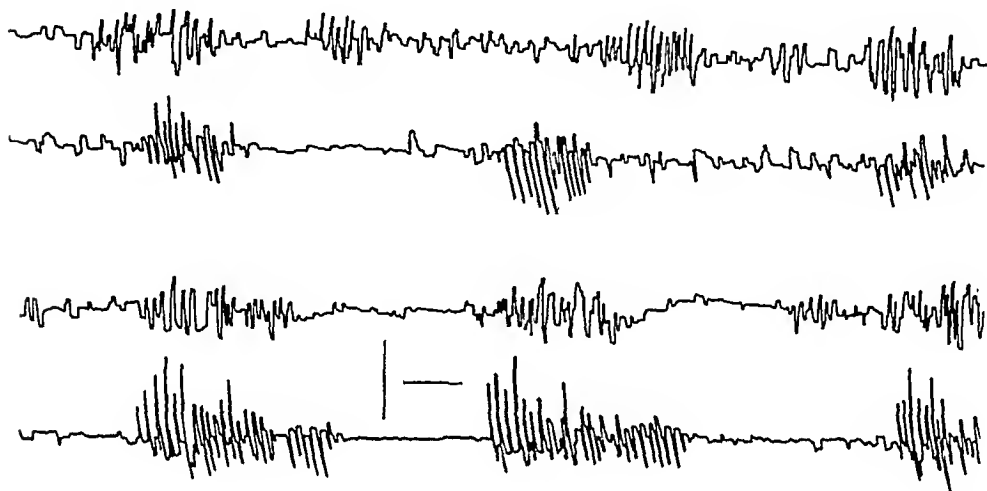


FIG. 7. Caudate nucleus (upper) and motor cortex (lower) records. Bipolar electrodes in each. Upper row before anoxia, lower row 45 secs. after release of a 52 sec. occlusion. Note imperfect synchrony before anoxia, more striking synchrony after.

brain preparation (Bremer, 1936; Bremer and Thomas, 1936; Bailey and Bremer, 1938) behaves much like the barbitalised one; and our present findings are comparable to those of Bremer except for the actual time scale. Since in the earlier experiments the blood supply was not completely eliminated (carotid occlusion only) or anoxia was produced by stopping artificial respiration, the longer intervals observed, as compared to the present ones obtained by sudden complete anoxia, are easily understood. Only a very partial or slowly developing anoxia could account for the long persistence of brain potentials and respiration found in the earliest work (Prawdicz-Neminski, 1925).

Survival times vary by a factor of four (over ten if all slow waves are included) from the shortest, in the cerebellar grey, to the longest, in the medulla. Arranged in order of decreasing times, structures fall into an anatomical sequence from "lower" to "higher" centers, or a phylogenetic one from older to newer (Pike, Guthrie, and Stewart, 1908a). The principal exception seems to be for the survival time of the cerebral cortex; which exception disappears in the revival time sequence (Heymans, *et al.*, 1937). The same general order, manifest when survival, revival or recovery times are considered, is met in mineral content (Alexander, 1938; Tupikova and Gerard, 1937) and in asphyxial degeneration determined microscopically; and, particularly, parallels



channels; and the changes in potentials of known structures were observed during and after anaemia.

The survival time (duration of occlusion necessary to abolish electrical activity) varied four-fold from one brain region to another, though consistent for each, the "highest" and the newest ones failing first. There are gradients of metabolic intensity in the encephalon paralleling developmental, structural, and functional ones.

The recovery time (interval between restoration of circulation and return of potentials) for any structure increases with duration of the anaemia and with the number of preceding anaemia periods. Under equivalent conditions the recovery times for various brain regions fall into the same sequence as their survival times.

Anaemia acts primarily via anoxia, though hypoglycaemia and hypercapnia contribute. (Hypoglycaemia hastens the action of occlusion but hyperglycaemia is without influence.) The time values for change in function following altered oxygen supply indicate relative respiration rates of the structures studied. These relative rates are in agreement with those estimated in other ways.

During advancing anoxia brain potentials pass through a phase of increased frequency and often amplitude, indicating a transient stimulation en route to depression. Recurring large spindles follow anoxia, especially in the motor cortex. Another sign of increased excitation is an improved synchrony of potentials in widely separated structures.

Synapses are not especially sensitive to anoxia since, following occlusion, optic impulses persist at the geniculate, in secondary neurons, after unevoked potentials in the cortex have disappeared. The geniculate rhythm and responses to visual stimuli disappear and reappear together.

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# STUDIES ON CORTICOHYPOTHALAMIC RELATIONS IN THE CAT AND MAN

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## INTRODUCTION

INTEREST in the hypothalamus has centered largely upon its function as an autonomic center mediating impulses which cause peripheral modifications of blood pressure, vasomotor states, visceral motility, etc., and upon the rôle of the cerebral cortex in inhibiting and augmenting hypothalamic functions. Experiments demonstrating release of cortical control of the hypothalamus, with resulting overactivity and "sham" emotional states, have been valuable in interpreting phenomena of emotional hyperactivity in man.<sup>1</sup> We have been interested in the reverse influence, namely the effect of hypothalamic activity upon the cerebral cortex in the intact animal, since an "emotional" influence on "thinking" is so commonly assumed in modern dynamic psychology.

## ANIMAL EXPERIMENTS

The hypothalamus of an intact animal can be stimulated without traumatizing nervous tissue by means of the following technique<sup>2\*</sup>

### STIMULATING TECHNIQUE

Cats were anesthetized with ether administered by tracheal cannula or, in most experiments, with nembutal, 65 mgm per kg body weight, intraperitoneally. The animals were fastened occiput down to an operating board by a special spring clamp which kept the snout down and the lower jaw maximally extended. The hypothalamus was approached by a trans-oral method. With experience, the soft tissue can be pierced by a probe in the proper location and spread apart. When the periosteum is stripped a small midline bleeding point may be seen in the posterior portion of the hard palate. This is an emissary vein lying in the rudiment of the old craniopharyngeal duct and hence just below the hypophysis and hypothalamus. A tapping instrument was used to make a few screw turns in the bone at this point and a small shell of hard bakelite threaded on the outside and with a ridge on its superior surface was screwed into place. The bakelite contained a nonpolarizing spiral of chloridized silver wire with a fresh wisp of cotton soaked with saline inserted in its core. The electrode did not pierce the bone. The silver wire, which extended through the superior surface of the bakelite as the primary lead, was entirely insulated by enamel.

In most of these experiments unipolar stimuli (induction shocks) were employed and the indifferent electrode was firmly attached to the shaven neck or screwed into the nasal bones. Carotid blood pressure and thoracic respiration were recorded as usual, and muscle movements, elevation of hair, dilatation of the pupils and movement of the nictitating membrane were observed. After the experiment the location of the electrodes was verified anatomically. In the majority of cases it was directly beneath the hypothalamus.

Forty-one cats were employed in these preliminary experiments. Rise in blood pressure was almost always obtained by passing induction shocks through the bone underlying the hypothalamus. Moderate stimuli (Harvard

\* In these first experiments Dr. Sam Stein, Fellow in Neuropsychiatry, gave valuable assistance.



inductorium, 3 volts in primary, secondary at 7 to 9 cm.) produced a rise of 30 to 40 mm. Hg., in most cases unaccompanied by changes in respiration, diaphragm spasm or somatic muscular movements (Figs. 1 and 2). In an



FIG. 1. Rise in blood pressure and increased respiratory rate resulting from induction shocks through the bone beneath the hypothalamus in the cat.



FIG. 2. Rise in blood pressure, increased cardiac rate and dyspnea during hypothalamic excitation from induction shocks passed through the underlying bone of the cat.

occasional animal isolated depression of blood pressure was observed. This atypical response could not be correlated with type of anesthesia, location of electrode or strength of current. No changes in blood pressure resulted from stimulation of the soft tissues or the periosteum of the hard palate, indicating that the blood pressure response was not a reflex to a painful stimulus. The heart rate was often accelerated or unchanged.

As previously found (Leiter and Grinker<sup>3</sup>), respiratory responses when present often consisted of a peculiar dyspnea. In some cases respiration was slowed or stopped. Usually the nictitating membrane retracted and the pupils dilated; only occasionally was a contraction of the pupils observed. These typical hypothalamic responses served to show that the hypothalamus can be stimulated through the bone in the intact animal,

and under barbiturate anesthesia; and they suggested the possibility that hypothalamic potentials might be recorded under the same conditions.

#### RECORDING TECHNIQUE

After obtaining positive responses to stimulation, the hypothalamic lead was connected to an amplifier. A similar lead to a second channel was screwed into the occipital bone or over the frontal lobes to record cortical potentials. A common indifferent lead, identical in structure to the above, was screwed into the nasal bones. The electrical apparatus was made for us by Mr. Franklin Offner of the University of Chicago.<sup>4</sup> The two balanced, five-stage (all push-pull) resistance capacity coupled amplifiers drove two cryostat graph ink-writing oscillographs (Offner and Gerard), of frequency range 0-150 vibration-per sec.; the time constant of the amplifiers was 0.5 sec. Low pass filter condensers were used in most experiments to remove frequencies greater than 25 per sec. In most experiments an amplification of 4 to 5 mm. per 100 microvolts ( $\mu$ v.) was used, although this varied somewhat.

Records from the cortical and hypothalamic regions (23 cats) are strikingly different so that either can be identified easily (Fig. 3).<sup>\*</sup> The alpha rhythm of the cortex was often disturbed by sudden spikes of moderate voltage. The alpha waves appeared in bursts at the usual 10 to 12 per sec. frequency and

\* In this and subsequent figures, simultaneous records from cortex and hypothalamus are illustrated with cortex in the upper tracing (C) and hypothalamus below (H). The time is constant: 17 mm. equal 1 sec. The perpendicular line represents the linear measurement of 100  $\mu$ v.

70 or more  $\mu\text{v.}$  in size; and sometimes interrupted by a few broad 3 per sec. waves of 50 to 60  $\mu\text{v.}$  intensity. The hypothalamus, however, showed an irregularly but frequently appearing wave of 0.18 to 0.25 sec. duration, occurring 4 to 5 per sec. and 50 to 60  $\mu\text{v.}$  in intensity. Superimposed on these were regular 13 per sec. waves of 12 to 15  $\mu\text{v.}$  When the slow waves were of low voltage, bursts of alpha waves could be seen from the hypothalamic lead, but these were feebler than, and not synchronous with, those from the cortex and were fewer in number.

The hypothalamus could be stimulated by induction shocks, with the amplifier disconnected. Potential recording was possible within 7 to 8 sec. after the end of such stimulation. The hypothalamic slow waves increased 25 to 50 per cent in voltage and were accelerated from 4 up to 5 to 7 per sec.

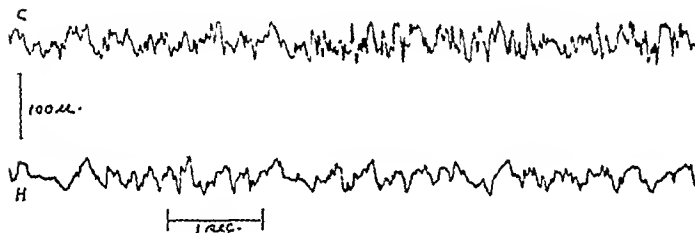


FIG 3 Typical cortical and hypothalamic action potentials in the cat under nembutal anesthesia (C, cortex and H, hypothalamus), both obtained through the intact bone. In the cortical tracing bursts of alphas are visible as well as occasional broad waves. The hypothalamic curve shows a broad 4 per sec. waves, superimposed on which are small 13 per sec. waves.

(Fig. 4). Giant regular cusp-like waves, of 150 to 200  $\mu\text{v.}$  appeared sporadically but frequently, and other large 1 to 2 per sec. waves less commonly. Occasional bursts of alpha waves were observed, especially after stronger stimulation, which tended to synchronize with those of the cortex (Fig. 4, series 4).

Stimulation of the hypothalamus also affected the cerebral cortex by initiating fast beta waves which disappeared after several seconds. Large spikes and cusps at 4 to 5 per sec. were seen after moderate stimulation. The bursts of alpha waves became longer in duration and more sharply defined against the background; and each wave increased in voltage by 20 to 30 per cent, and became more regular and less broken by secondary waves. The cortical rhythm thus became plainer; for example, it was clear 40 to 50 per cent of the time before stimulation and 70 to 90 per cent after. Stronger currents tended to synchronize cortex and hypothalamus.

The hypothalamus was destroyed by piercing the bone under it and en-

circling it with a probe (Fig. 5). The result was a spectacular dropping out of almost all fast and slow waves. The alpha waves were reduced in voltage, but they became of greater duration, especially in the hypothalamic lead, and between their bursts only a few aberrant spikes appeared. Several minutes after the destruction, the alpha waves recovered in intensity and their bursts

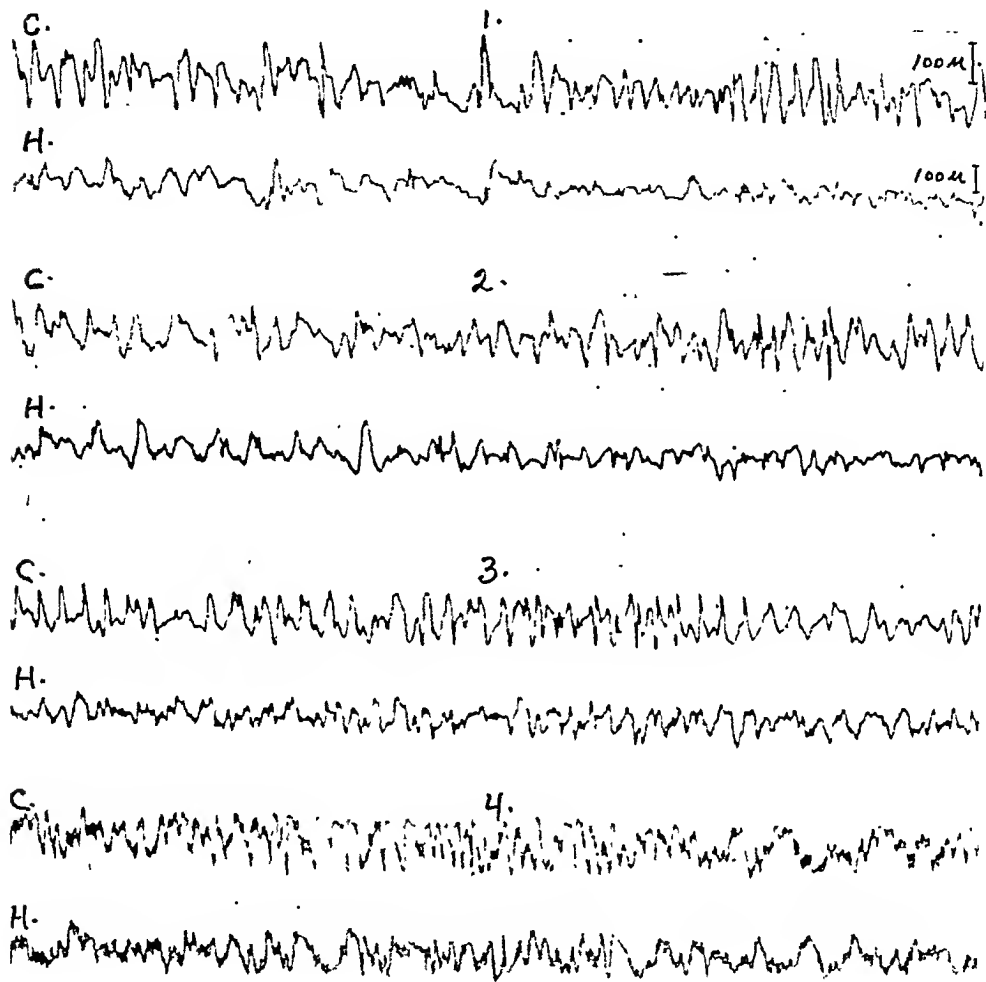


FIG. 4. The effect of stimulation of the hypothalamus of the cat through the bone: (1) before stimulation, (2) after stimulation with secondary coil of inductorium at 6.5 cm., (3) after stimulation with coil at 5 cm., (4) the same as (3) but with resulting partial synchrony of curves.

became sharply demarcated and synchronous in both leads. Stimulation of the base of the brain no longer affected cortical activity in the typical way, although in some instances it caused the alpha waves in both leads to become larger and more like spikes. The synchrony at both leads suggested that the cortical rhythms were spreading directly to the hypothalamic lead.

## PHARMACOLOGICAL EXPERIMENTS

The effects of adrenaline, eserine, ergotamine, pilocarpine, nembutal and metrazol on cortical and hypothalamic rhythms were next studied

**Adrenaline** (Fig 6) After injection of 0.4 cc of 1/1000 per cent adrenaline intravenously the cortical rhythm changed from fairly regular alpha waves 8 to 10 per sec and 60 to 70  $\mu$ v to less regular ones, 10 to 14 per sec and 100 to 110  $\mu$ v. Many fast waves also appeared and the alpha group showed rapid bursts with little interval between them. In 3 min the fast waves disappeared

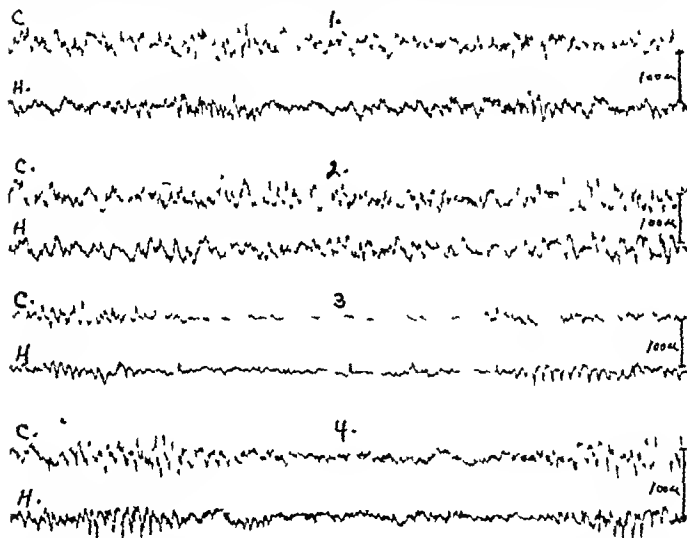


FIG 5 The result of destruction of the cat's hypothalamus on currents obtained through the bone (1) before destruction without stimulation (2) stimulation with second ary coil at 8 cm (3) thirty seconds after destruction of the hypothalamus (4) stimulation of the hypothalamus as in (2) after destruction

and the original rhythm returned but with the alpha waves still large. The hypothalamic waves at 4 per sec and about 30  $\mu$ v, with occasional alpha sequences of 4 or 5 waves in 0.5 sec at 40  $\mu$ v, promptly gave way to waves of alpha frequency at 60  $\mu$ v somewhat synchronized with the cortical alpha waves along with faster waves. Three minutes later the alpha and fast waves had disappeared and the 4 per sec rhythm reappeared and were larger than prior to injection. Adrenaline thus acted upon both the hypothalamus and cortex just as a powerful electrical stimulation of the hypothalamus. Perhaps the cortical effect is secondary, in both cases, to hypothalamic stimulation.

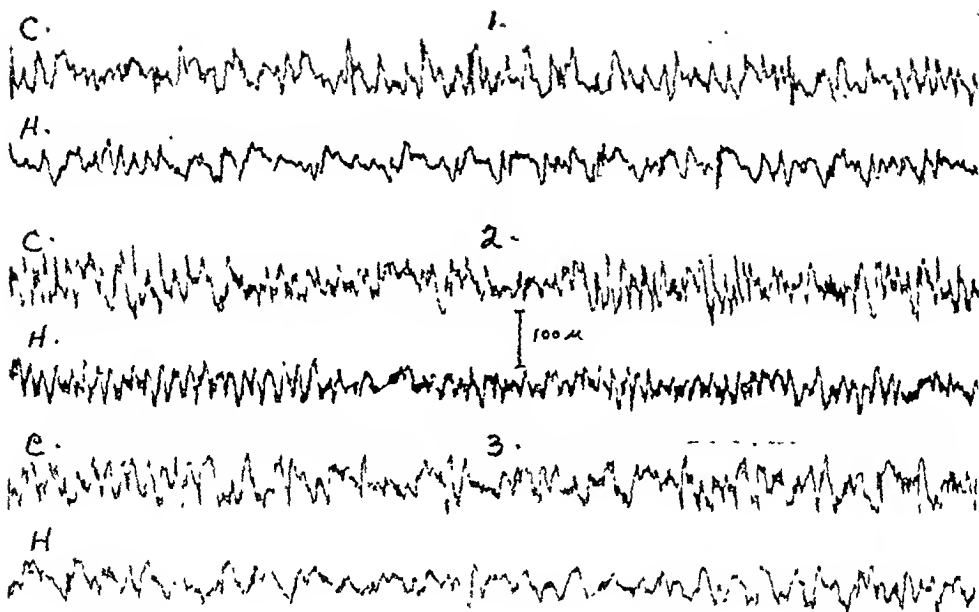


FIG. 6. The effect of 0.4 cc. of 1/1000 per cent adrenaline intravenously in the cat: (1) before injection, (2) immediately after injection, (3) three minutes after injection. Note the similarity of the effect to that of strong electrical stimulation of the hypothalamus as in Fig. 4, series 4.

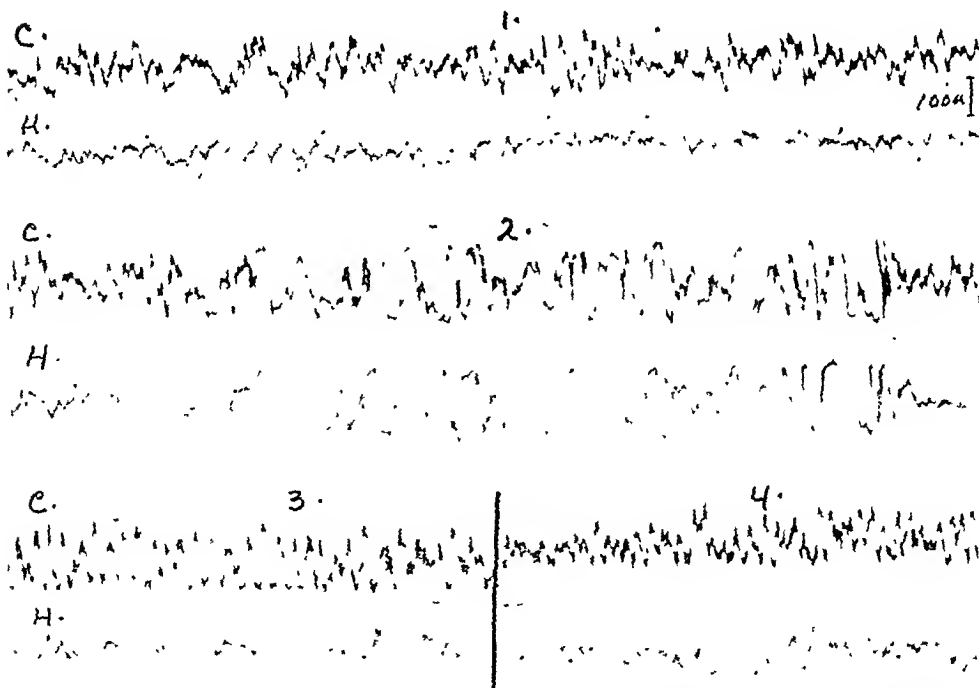


FIG. 7. The effect of 1.3 mgm. eserine injected intravenously in the cat: (1) before injection, (2) immediate excitement period, (3) 2.5 min. after injection, (4) 18 min. later.

*Eserine* (Fig. 7). Intravenous injection of 1.3 mg. of *eserine* caused slit-like pupils, marked ocular nystagmus and physical unrest. Hypothalamic and cortical potentials became synchronous and developed bursts of irregular coarse waves at 4 per sec. and more than 200  $\mu$ v. in amplitude, with feebler waves at 15 or more per sec. superimposed. These bursts paralleled physical excitement and strongly suggested hypothalamic stimulation. Two minutes

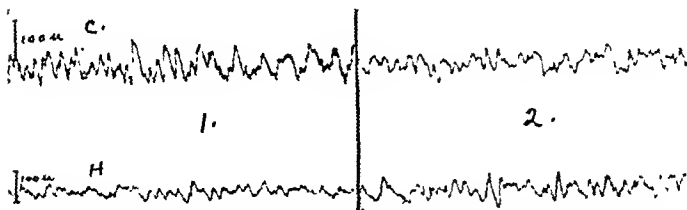


FIG. 8. The effect of 5 mgm. ergotamine injected intravenously in the cat, repeated in sixteen minutes. (1) before injection, (2) eight minutes after second injection.

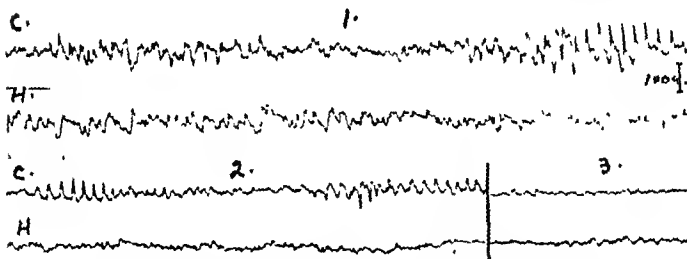


FIG. 9. The effect of 8 mg. pilocarpine injected intravenously in the cat: (1) before injection, (2) 16 sec. after injection, (3) 1 min. later.

later the hypothalamus quieted down to its normal pattern but with approximately double the pre-injection voltage; while the cortex continued to beat steadily and with great intensity for as long as twenty minutes before gradually declining. The cortical pattern consisted of giant alpha waves of 200  $\mu$ v. intensity at 9 to 10 per sec., in regular steady rhythm without bursts (Fig. 7, series 3). After twenty minutes, the waves, still regular and continuous, had declined to 150  $\mu$ v. *Eserine* thus produces a conjoint excitation of cortex and hypothalamus. The cortex first takes over the typical hypothalamic pattern, and in exaggerated intensity, and then returns to a normal cortical pattern, but still of greatly increased intensity. The hypothalamus shows a brief but intense increase in activity and quickly returns to its resting state.

*Ergotamine* (Fig. 8). Five mgm. of ergotamine were injected intravenously and the dose repeated in 16 min; only after another 8 min. were 10 per sec. alpha waves of 80 to 90  $\mu$ v. in the cortex slowed to 6 to 7 per sec. and reduced to 50  $\mu$ v. No fast waves appeared. The hypothalamic response, in contrast to that of the cortex, was excitatory and resembled greatly the effects of moderate stimulation.

*Pilocarpine* (Fig. 9). Eight mgm. of pilocarpine were injected intravenously; this was followed by sweating, salivation, constriction of the pupils (from 7 mm. to 3 mm. in diameter), and relaxation of the nictitating membrane. The effect on the cortex and hypothalamus was immediate. In 16.5

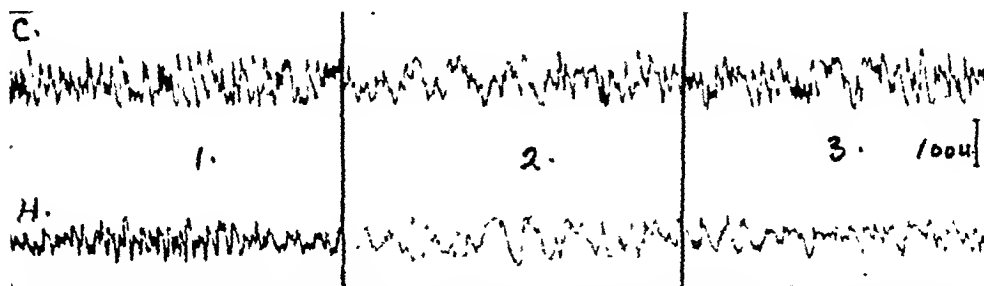


FIG. 10. The effect of 100 mg. nembutal injected intravenously in the cat: (1) before injection, (2) after injection, (3) the effect of stimulation after nembutal injection.

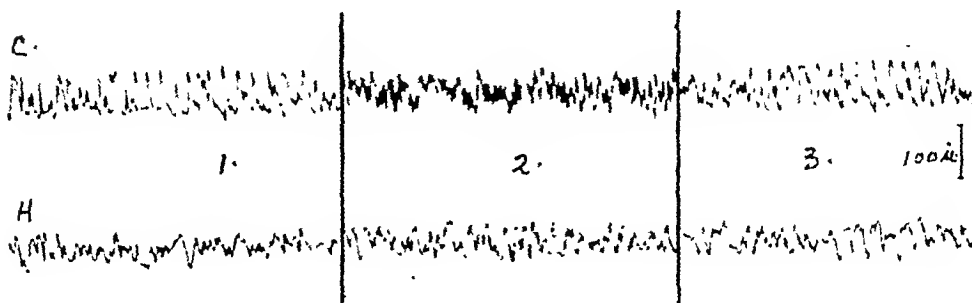


FIG. 11. The effect of 1 cc. of 10 per cent metrazol injected intravenously in the cat: (1) before injection, (2) 20 sec. after injection, (3) 60 sec. after injection.

sec. the hypothalamus showed barely measurable rapid waves at about 20 per sec., and after another minute the tracing was almost a straight line. The cortex showed the same initial pattern as the hypothalamus, but the pattern was interrupted by bursts of waves lasting about 1 sec. and recurring in 5.5 to 6 sec. These bursts were only half the size of the original alpha waves and more spike-like, but they retained their original frequency. After another minute these bursts had disappeared and the cortical tracing became also a straight line.

*Nembutal* (Fig. 10). One hundred mgm. of nembutal intravenously were superimposed on the original intraperitoneal injection. All fast waves were

promptly abolished, and the slow waves of both cortex and hypothalamus were slowed and enhanced. The effect was that of a slowing in time of 30 to 40 per cent with little change in intensity. The effect was still present 45 min. later, when hypothalamic stimulation seemed to counteract partly the nembutal effect.

*Metrazol* (Fig. 11). Intravenous injection of 1 cc. of 10 per cent metrazol solution resulted in very rapid respirations and convulsive movements of the forepaws and neck muscles. Both cortical and hypothalamic records showed signs of stimulation with abundant fast waves and increase in both preexisting frequencies (cortex, from 9 to 15 per sec; hypothalamus, from 9 to 13). Cortical potentials decreased 20 per cent in amplitude and the hypothalamic ones increased by the same amount. After one minute the cortical potentials had returned to normal and those from the hypothalamus were of normal configuration though still of greater frequency and intensity.

### HUMAN EXPERIMENTS

In the human the hypophysis and its overlying hypothalamus lie above or just behind the variable sphenoidal air sinus. This sinus ends posteriorly beneath the anterior clinoid processes or at most extends to a point below the middle of the floor of the sella turcica. It does not normally reach the posterior clinoids. The hypothalamus is thus closest to the base of the skull over the sella turcica and extending backward for a few millimeters. Between it and the dura, firmly attached to the bone, is a small subarachnoid space. Occasionally the anterior portion of the interpeduncular cistern extends this far anteriorly.

### TECHNIQUE

The hypothalamic lead consisted of a sharply tipped steel drill rod 3 mm. in diameter and 16 cm. long with a slight upward concavity at its terminal third (Fig. 12). The rod was insulated to within 2 mm. of its tip with celluloid and Duco-cement and the exposed tip heavily silver-plated. A flexible enameled copper wire connected it with the amplifier. The cortical leads were silver spirals in the form of discs covered with electrode jelly, and fastened to the scalp with collodion. The resistance of such leads is less than 5,000 ohms. In some experiments silver wire earrings connected to a common wire were used as a reference lead for both occipital and hypothalamic leads. Insertion of the hypothalamic lead was easily accomplished. We are indebted to Dr. Samuel J. Pearlman for invaluable help in teaching us the technique. With the patient sitting the nasal mucous membranes were cocaineized, the applicator being inserted to the posterior pharyngeal wall. At first an endoscope was placed in one nostril and the lead inserted with direct visualization by way of the other nasal passage. Later visualization became unnecessary and only one nostril was cocaineized. The lead was passed carefully through the nasal passage and tipped upward when the posterior pharyngeal wall was reached (the exposed end of the electrode lay above and against the lower lip) to engage the pharyngeal mucosa at the junction of the roof of the pharyngeal vault and the posterior pharyngeal wall. With a forcible movement the needle tip was pushed through the mucous membrane, submucosa and periosteum into the sphenoid bone. A slight crunching sound and decreased mobility of the electrode indicate when it is firmly imbedded. The subjects feel a slight twinge of pain on insertion of the electrode but this soon passes off and they walk about comfortably for hours if necessary, with no interference with speech or swallowing.

The lead is removed with a sudden jerk and no subsequent antiseptic is necessary. The slight wound has never caused subsequent difficulty due to infection or hemorrhage. Two difficulties may be mentioned. If the electrode is not inserted high enough into the



vault a few strands of pharyngeal muscle are engaged and their action potentials obscure those from the hypothalamus. A large sphenoidal air sinus or an unusually shaped base of the skull mitigate against a successful registration of hypothalamic waves. The subjects lay relaxed and motionless on a couch in a darkened copper-screened room with eyes shut. For stimulation, the secondary coil (Harvard inductorium, 3 volts in primary) was pushed in during 10 sec. to 1 cm. (to avoid startle) and tetanization continued 5 to 20 sec. longer.

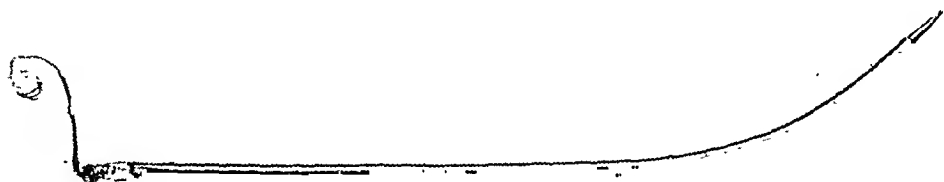


FIG. 12. The electrode used in stimulating the human hypothalamus through the underlying sphenoid bone.

Warning of a stimulation was given a few seconds in advance and only 2 or 3 stimuli applied to one person. Subjects for these experiments were obtained from general medical wards (excluding patients with debilitating or cardiac disease), or from the neuropsychiatric service.

#### *Responses to stimulation*

Stimulation of the hypothalamus produced a marked dilatation of the pupils, generalized hyperemia of the skin, copious perspiration, and a great rise in blood pressure. In one case the pressure rose 80 mm. Hg. during stimulation and took several minutes to return to normal. Evacuation of the urinary bladder occurred once, and in one subject body temperature rose to 103°F., and remained elevated for several days, without leucocytosis or other sign of infection. Strong stimuli evoked gradually increasing tonic spasms of the trunk and extremities, which did not outlast the current, sometimes accompanied by cyanosis. The spasms appeared only after stimulation had continued for several seconds and probably were due to spread to the cerebral peduncles or mesencephalon. Stimulation was painful due to current spread but subjects were willing to bear it for such brief periods. Controls showed that the responses described were not due to sensory stimulation.

Apart from transient pain responses, sometimes anxiety appeared during stimulation, and it persisted with crying and expressions of fear often for some minutes. In one subject protracted sobbing occurred. Several patients saw their lives pass before their eyes, as has been described in drowning. In general, the affective state accompanying hypothalamic stimulation could not be correlated with the rage attacks in human encephalitics, the manic responses from operative manipulation of the hypothalamus or the sham rage of cats.

## CORTICOHYPOTHALAMIC RELATIONS

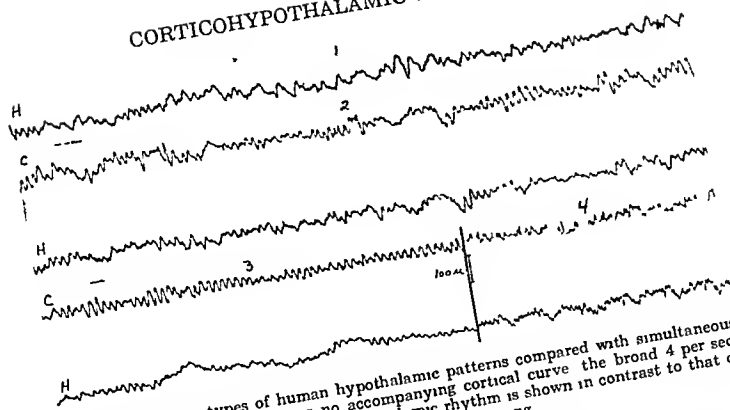


FIG 13 Four types of human hypothalamic patterns compared with simultaneous cortical tracings. In (1) there is no accompanying cortical curve the broad 4 per sec waves are characteristic, (2) alpha hypothalamic rhythm is shown in contrast to that of the cortex, (4) shows undulations in the hypothalamic tracing

Cortical potentials were more or less dominated by the 10 per sec rhythm which was also frequently clear in the hypothalamic record (Fig 13). Hypothalamic alpha waves tended to accompany cortical waves, but they were not as frequent and never of as high a voltage (Fig 13, series 2). Besides the

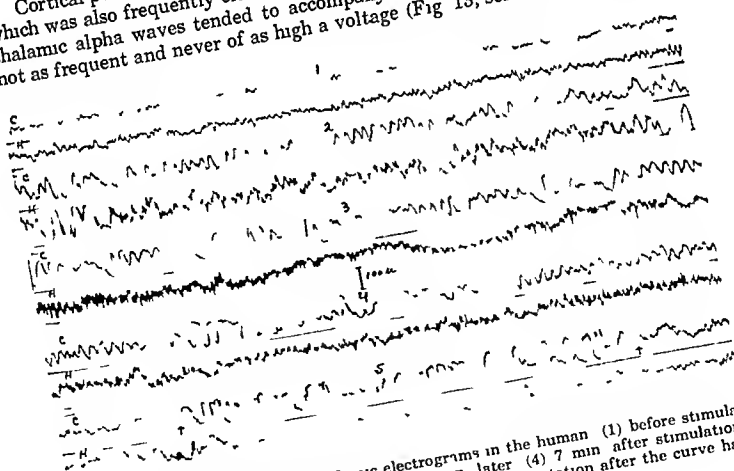


FIG 14 Cortical and hypothalamic electrograms in the human (1) before stimulation, (2) immediately after stimulation, (3) 4 min later (4) 7 min after stimulation, (5) 9 min after stimulation showing a recurrent wave of excitation after the curve had returned to its pre stimulation level (within arrows)

alphas there were slower coarser 4 to 6 per sec. waves of 30 to 50  $\mu$ v. intensity in the hypothalamus (Fig. 13, series 1); and occasional larger waves and coarse undulations occurred once every 0.6 to 0.8 sec. (Fig. 13, series 4). In general

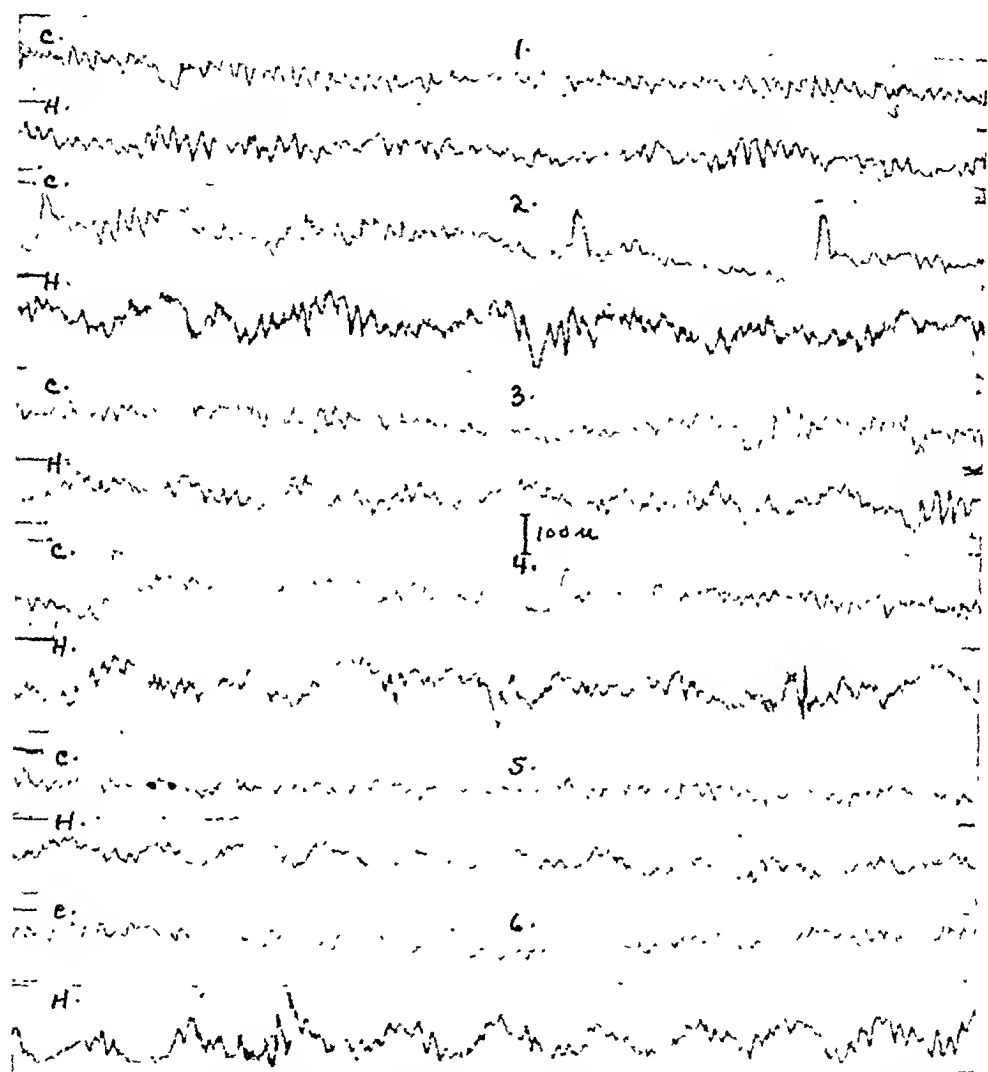


FIG. 15. Cortical and hypothalamic electrograms in the human: (1) before stimulation, (2) immediate effect of stimulation, (3) 2 min. later, (4) 4 min. after stimulation, (5) 5 min. after stimulation, (6) second stimulation with little effect on cortex.

the human "resting" hypothalamus beat like that of the cat with 4 per sec. waves as the "typical" characteristic, but for each subject the hypothalamic record was more individual than that of the cortex and probably more characteristic than a given cortical pattern.<sup>5</sup> In several cases only alpha waves appeared before stimulation, but following it they were replaced by the

...pha waves, in contrast to those  
 ...continuous with the eyes open  
 than with them shut (Fig. 18).

### Electrograms

*Hypothalamus.* Stimulation was followed by increased excitation in the hypothalamic electrogram (Figs. 13-16). A marked increase of fast waves uncountable at the ordinary recording speed almost always thickened the record for several minutes and disappeared gradually (Figs. 14<sup>2,3,4</sup> and 15<sup>2</sup>). Immediately after stimulation the waves became extremely irregular and any alpha rhythm which had been present completely disappeared. The 4 per sec. waves also became irregular and usually doubled their amplitude. In some persons an undulation appeared at 70 per min. at 30  $\mu$ v. intensity. This was

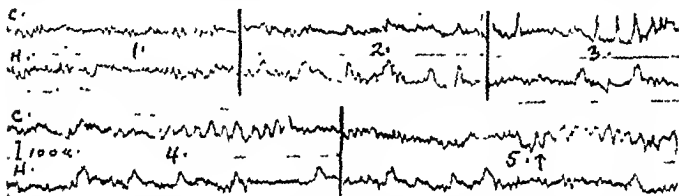


FIG. 16. Cortical and hypothalamic electrograms in the human: (1) before stimulation, (2) immediately after stimulation, (3) 4 min. after stimulation, (4) 5 min. after stimulation, (5) 7 min. after stimulation, showing a burst of cortical excitation in the midst of a quiescent period.

considerably slower than and not to be mistaken for the pulse rate (Fig. 15<sup>5,6</sup>). Sometimes the hypothalamic rhythm was interrupted by giant waves (200  $\mu$ v.) and the entire curve for several minutes was synchronous with that of the cerebral cortex (Fig. 17<sup>2</sup>); as in the cat after strong hypothalamic stimulation.

The late effects of hypothalamic stimulation were equally interesting. The 70-per-min. wave sometimes lasted several minutes, disappearing and returning again. More frequently the large giant waves disappeared and a modified alpha rhythm of low voltage reappeared, but interrupted irregularly by large rounded slow waves at 2 per sec. (Fig. 16). This pattern might continue for several seconds, or fade and return. An occasional train of fast waves was often seen, and occasionally large spikes or cusps appeared for 1 to 2 sec. and were followed by quiescent periods of a minute or more. The general impression was that, after the initial excitation had subsided, increased hypothalamic activity reappeared in short, recurrent, irregular periods.

*Cortex.* As a result of hypothalamic stimulation the cortical alpha rhythm was sometimes interrupted by large rounded 100 to 120  $\mu$ v. waves, lasting 0.3 sec. and appearing once in 2 or 3 sec. (Figs. 15 and 16). These continued

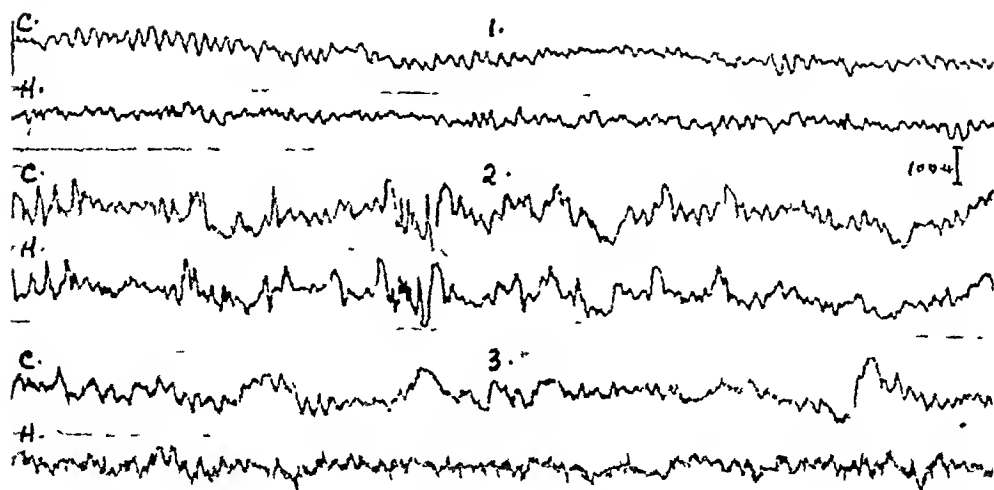


FIG. 17. Cortical and hypothalamic electrograms in the human: (1) before stimulation, (2) synchronized immediate effect of strong stimulation, (3) 6 min. after stimulation reappearance of excitation after curve had become quiescent as in (1).

to appear sporadically for several minutes, becoming more and more infrequent. Large irregular undulations also appeared after stimulation and gradually straightened out to normal during several minutes (Fig. 17). Large rounded waves, with the alphas superimposed, sometimes occurred 6 to 8 min. after stimulation. In a few cases, spikes of 100  $\mu$ v. and 4 per sec. appeared in the cortex in phase with the rounded large waves in the hypothalamus, even 4 or 5 min. after stimulation. The alpha waves themselves were gradually slowed, to 5 per sec. and intensified, as much as four fold. Giant waves of 200 to 250  $\mu$ v. appeared as individuals, later in groups lasting for several seconds interspersed between large alpha waves, and still later in ten second trains erupting in the midst of a normal rhythm (Figs. 14 and 16).

An attempt was made to excite the hypothalamus by strong emotions (Fig. 19). A subject was told that a sex habit, regarding which he had considerable anxiety, had probably irreparably damaged him. Both cortical and hypothalamic curves became irregular and partially synchronous, and giant

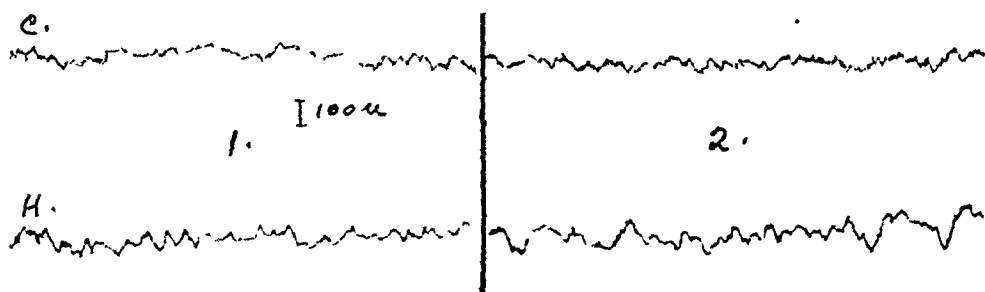


FIG. 18. In (1) subject has his eyes shut; in (2) he has opened his eyes.

## CORTICOHYPOTHALAMIC RELATIONS

waves and plateaus with frequent cusps appeared. After several minutes the hypothalamus was still beating irregularly with numerous spikes and cusps (Fig. 19, series 3 at arrow). An electrical stimulation of the hypothalamus in-

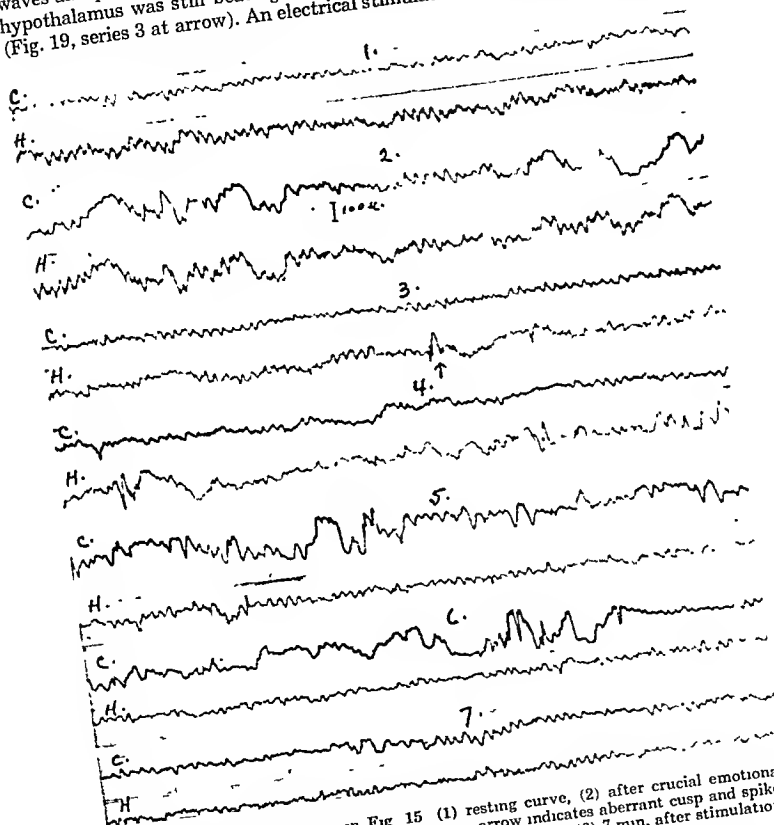


FIG. 19. Same patient as in Fig. 15 (1) resting curve, (2) after crucial emotional stimulus administered verbally, (3) reassurance, arrow indicates aberrant cusp and spike, (4) electrical stimulation, (5) 6 min. after electrical stimulus, (6) 7 min. after stimulation, (7) return quiescent stage ten minutes after stimulation.

duced immediate changes in this region and delayed ones in the cortex, appearing 6 min. after stimulation and subsiding in another four, which paralleled those resulting from the emotional stimulus (Fig. 19).

## DISCUSSION

This method for stimulating the hypothalamus through the base of the cranium is useful in animals since it is simple, easily performed, requires no operation, and can be used acutely on a conscious animal. It is adapted rather for study of the hypothalamus as a whole and does not permit the localization possible with the Horsley-Clarke instrument. In the intact human, however, this is the only method available for stimulating the hypothalamus or leading off its action potentials. It should prove possible to follow the influence of ideational stimuli with emotional coloring, as here reported, and to study the effects of direct electrical stimulation of the hypothalamus on the peripheral autonomic system by observing heart-beat, gastro-intestinal motility, secretion and vascular changes, bladder and ureteral tone, temperature, sleep, etc. The hypothalamic lead may also aid in the study of excitatory processes in epilepsy and irritative lesions, assist in more accurate localization of intracranial neoplasms and further our knowledge of corticohypothalamic relations in mental disturbances.

The spontaneous potentials of the cat and human hypothalamus are predominantly slow waves at 4 to 5 per sec. and at 0.9 per sec. Small waves at 13 to 15 per sec. and the alpha rhythm are variable. The alpha waves probably originate in the hypothalamus, for they are of different frequency and regularity than the cortical ones, though after destruction of the hypothalamus cortical alpha waves seem to reach the basal electrode.

Stimulation of the hypothalamus evokes a massive discharge which persists or reappears for minutes after the stimulation is over. This suggests that this structure serves as a reservoir for prolonged excitation and has a chronic influence on brain and periphery. Affect-laden ideational stimuli similarly cause hypothalamic excitation which precedes and outlasts the cortical ones. The results indicate a "driving" of cortex by hypothalamus parallel to the well recognized overwhelming of intellectual processes by emotional activity.

The changes in cortical potentials produced by hypothalamic excitation, increased voltage of the alpha waves and appearance of large, slow waves are suggestive of the "disintegrated curves" described for schizophrenia and organic brain disease.<sup>6</sup> The alpha pattern of the normal human cortex is not fixed and can be profoundly modified by hypothalamic stimulation even to the point of resembling pathological curves. The more detailed psychiatric parallels to and interpretations of these findings will be reported elsewhere.

## SUMMARY

1. A method has been described for stimulating the hypothalamus and recording its electrical activity in the intact cat and man.
2. The hypothalamic electrogram is specific and differs from the cortical electrogram.
3. Epinephrine, eserine, ergotamine, pilocarpine, nembutal and metrazol produce characteristic changes in these electrograms.

## CORTICOHYPOTHALAMIC RELATIONS

4. Electrical stimulation of the hypothalamus increases the hypothalamic potentials at once and in recurrent long-lasting bursts. A similar effect on the cortex is probably secondary to the hypothalamic one.
5. Ideational emotion-laden stimuli produce effects on hypothalamus and cortex similar to those elicited by electrical stimulation of the hypothalamus.
6. Strong electrical or emotional stimuli result in extensive synchronous discharge of hypothalamus and cortex.

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# EFFECTS ON ELECTROENCEPHALOGRAM OF VARIOUS AGENTS USED IN TREATING SCHIZOPHRENIA\*

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THE GROSS LACK of information concerning the mechanism of action of various agents now used in treating schizophrenia has been a stumbling block in otherwise rapid progress toward understanding this disorder. The present study was undertaken with the object of seeing what changes, if any, were caused in brain wave patterns of schizophrenic patients subjected to insulin hypoglycemia, metrazol, intravenous sodium amytal, carbon dioxide inhalation and emotional stimulation. Although electroencephalograms obtained from schizophrenic patients fall within normal limits, there is a definite tendency towards a weak alpha (10 per sec.) rhythm in this disorder.<sup>1,2,3,4,5</sup> Hoagland, Rubin and Cameron<sup>6</sup> and Yeager and Baldes<sup>2</sup> have also shown that 1 to 5 per sec. delta waves are usually increased during the more severe phases of the schizophrenic illness. The significance of these characteristics of the electroencephalogram in schizophrenia will be discussed later.

## RESULTS

*Insulin hypoglycemia.* Electroencephalograms (EEG) were obtained during insulin hypoglycemia in 15 schizophrenic patients. Twelve of these cases showed a definite weakness of the alpha rhythm before treatment (Fig. 1A). In the initial excitatory stages of the hypoglycemic reaction, the alpha rhythm was strengthened (Fig. 1B), and then as the reaction deepened into coma, the alpha waves were replaced by 1 to 5 per sec. delta waves characteristic of depressed cortical activity (Fig. 1C). Termination of the hypoglycemia by glucose was followed within 1 to 3 hours by a "rebound" strengthening of the alpha rhythm of variable duration in 10 of the 12 cases showing a weak alpha rhythm before treatment (Fig. 1D). Gerard<sup>7</sup> and Bremer and Thomas<sup>8</sup> have demonstrated a similar post depression enhancement of the cortical rhythms in animals.

Although clinical improvement was maintained in 9 of the cases responding to treatment, the alpha rhythm always reverted to its pretreatment level within from 1 to 4 weeks after discontinuing the treatment (Fig. 1E). The 1-to-5 per sec. delta waves were present in 6 of these 15 cases before treatment. They were eliminated by the treatment with no recurrence, except in one case that relapsed and again showed delta wave activity. This is in agreement with the findings of Hoagland, Rubin and Cameron.<sup>6</sup>

\* This investigation was carried out for the most part at the Eastern State Hospital, Medical Lake, Washington, and was financed by a grant from the Committee on Scientific Research of the American Medical Association.

*Metrazol.* It is difficult to study the effect of metrazol on the EEG because it is virtually impossible to record during the convulsion. Small subconvulsive doses of metrazol, however, increase alpha wave activity (Fig. 2B) and the postconvulsive depression is followed by a temporarily enhanced alpha rhythm similar to that following insulin coma (Fig. 2C). Here again the alpha

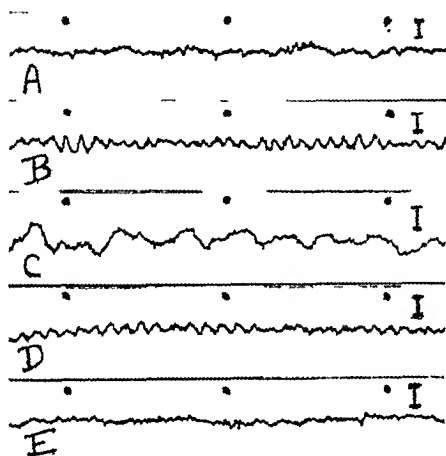


FIG 1 Record from a schizophrenic patient undergoing insulin shock treatment A Before insulin B Strengthening of alpha rhythm during initial excitatory stages of hypoglycemic reaction C Large 1 to 5 per sec delta waves associated with hypoglycemic coma D Two hours after termination of the hypoglycemic reaction "Rebound" activation of alpha rhythm E Three weeks after discontinuing insulin hypoglycemia treatment The record has reverted to its pretreatment appearance, although the patient has maintained his clinical remission The slow 1 to 5 per sec delta waves are less in evidence than in A The dot time markers are in seconds and the vertical measure at the side represents 50 $\mu$ v potential This and subsequent records are read from left to right

wave activity eventually reverts to its pretreatment level after treatment (Fig. 2D). Similar changes in the EEG following the injection of metrazol (or its physiological equivalent, camphor) have been described by Fischer and Lowenbach<sup>9</sup> in animals and Gibbs, Gibbs and Lennox<sup>10</sup> in man.

*Intravenous sodium amytal* Sodium amytal given slowly intravenously in schizophrenic patients (Fig. 3) accentuates the alpha rhythm during the prenarcoctic stage of its action. This runs parallel to the clinical improvement

with increased accessibility and rapport. As medication is continued, and the patient becomes drowsy, the alpha waves break up into faster, more irregular waves, interspersed with delta waves.

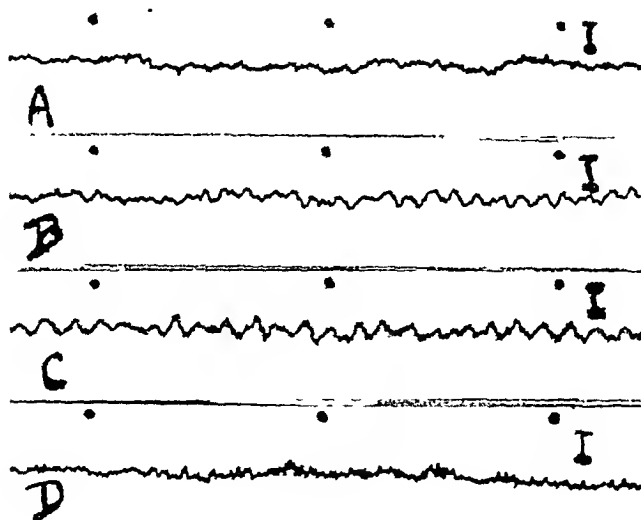


FIG. 2. Record from a schizophrenic patient. A. Before metrazol. B. During administration of subconvulsive dose of metrazol. C. 2 hours after metrazol convulsion, and D 5 days after last metrazol convulsion. The alpha rhythm is temporarily strengthened by the metrazol.

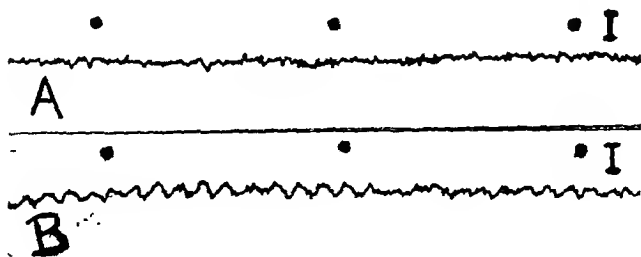


FIG. 3. Record from a schizophrenic patient. A before and B after subnarcotic dose of sodium amytal given intravenously.

*Carbon dioxide inhalation.* The inhalation of carbon dioxide also produces an accentuation of the alpha rhythm during the preliminary excitatory stages of its actions on schizophrenic patients (Fig. 4B). If unconsciousness is produced, the alpha rhythm again breaks up into fast waves superimposed on slower delta waves (Fig. 4C).

*Emotional stimulation.* There are many different types of emotional stimulation. Strong anxiety or agitation seems to preclude the development of an alpha rhythm.<sup>1</sup> On the other hand, milder, anticipatory, interest-producing,

and enthusiasm-arousing emotions, such as those caused by visits from relatives, the anticipation of going home, or the excitement of the first few weeks in a new environment, seem to strengthen the alpha rhythm (Fig. 5). Inter-

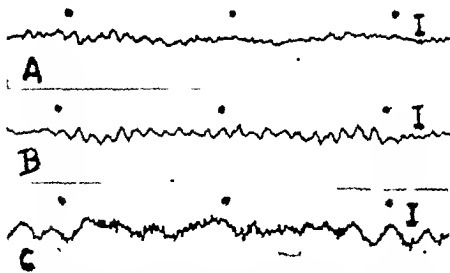


FIG 4 Record from a schizophrenia patient A before, B during the initial excitatory phase and C during coma produced by the inhalation of carbon dioxide

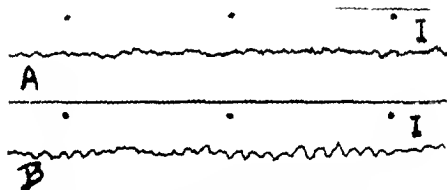


FIG 5 Record from a schizophrenic patient A before and B after being told that he was going to be discharged from the hospital Shows effect of mild emotional stimulation on the alpha rhythm

estingly enough it is just this type of interest-arousing affective situation that seems temporarily to help schizophrenic patients the most.

#### DISCUSSION

It is apparent that the agents commonly used to influence the schizophrenic process favorably seem temporarily to strengthen the weak alpha rhythm found in this disorder. One can only speculate concerning the significance of this finding. The work of Adrian<sup>11</sup> strongly suggests that alpha waves are produced by neurons of the resting visual cortex beating in unison over an area of at least one centimeter in diameter. A weak alpha rhythm, therefore, would indicate poor neuron synchronization<sup>12 13</sup> and, inasmuch as brain wave patterns seem to be inborn,<sup>5 11 15</sup> one might reasonably conclude

that poor cortical neuron synchronization is an inherent neurophysiological characteristic of schizophrenic patients.<sup>16</sup>

Gerard<sup>12</sup> and Jasper<sup>17</sup> have shown that cortical rhythms are strongest at certain optimum levels of excitation above which, or below which, the rhythms drop out. That the weak alpha rhythm of schizophrenia is due to a low rather than a high level of excitation is indicated by the fact that the agents investigated all exert their beneficial clinical effect on the schizophrenic symptoms during the preliminary (or postcomatose) excitatory stage of their action on the cortex and the alpha rhythm. It is probable that insulin, metrazol, sodium amytal and carbon dioxide depress cell oxidation with resulting anoxia and an increase in excitation followed by depression of the cortical neurons.<sup>12,18,19,20,21,22</sup> The action of emotional stimulation is less easily understood, but it possibly results from activation of the cerebral cortex by the diencephalon.<sup>16</sup>

The failure of the various treatment procedures to maintain a strengthened alpha rhythm would appear especially significant. This strongly suggests that the treatments used thus far are only temporary in their action, and that they fail to produce a lasting alteration in the fundamental neurophysiological defect of the weak alpha rhythm found in schizophrenia. As soon as the treatment is finished, the alpha waves return to their original pretreatment level, although a clinical remission may appear to have occurred.

### SUMMARY AND CONCLUSIONS

1. Although brain waves from schizophrenic patients fall within normal limits, there is a definite tendency toward a weak alpha rhythm in this disorder.

2. This weakness of the alpha rhythm in schizophrenia would appear to be an inborn neurophysiological characteristic of schizophrenia. The alpha rhythm is temporarily strengthened by insulin hypoglycemia, metrazol, intravenous sodium amytal, carbon dioxide inhalation and emotional stimulation—agents which sometimes seem favorably to influence the schizophrenic process.

3. The failure of these agents permanently to strengthen the alpha rhythm in schizophrenia suggests, however, that they produce only temporary benefit. This may be sufficient to cause a remission, but the fundamental neurophysiological defect evidently persists in a latent form even after "successful" clinical treatment.

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